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(71) Applicants: FUJIAN HAIXI PHARMACEUTICALS

CO., LTD [CN/CN]; 20 North Jinzhou, Jinshan Industrial
Park Cangshan District, Fuzhou, Fujian 350002 (CN).
KANG, Xinshan [CN/CN]; 30-C-301 Tianbaoyuan Liuli,
BDA, Beijing 100176 (CN).

(72) Inventors: WANG, Ruyong; 20 North Jinzhou, Jinshan
Industrial Park Cangshan District, Fuzhou, Fujian 350002
(CN). ZHU, Xizhen; 20 North Jinzhou, Jinshan Industrial
Park Cangshan District, Fuzhou, Fujian 350002 (CN).
KANG, Xinshan; 30-C-301 Tianbaoyuan Liuli, BDA,
Beijing 100176 (CN).

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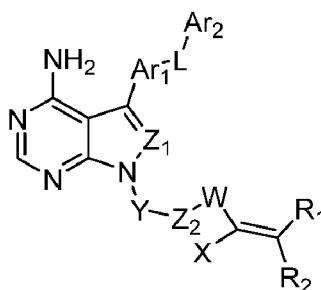
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(54) Title: INHIBITORS OF BRUTON'S TYROSINE KINASE



Formula (I)

(57) Abstract: Described herein are compounds and their applications with Bruton's tyrosine kinase inhibitory activity. The described compounds comprise at least a compound of Formula (I), or pharmaceutically acceptable salts thereof. Also described herein are methods for synthesizing such compounds, and their applications in the treatment of diseases: autoimmune diseases or conditions associated with aberrant B-cell proliferation such as rheumatoid arthritis, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions.

THE DESCRIPTION

INHIBITORS OF BRUTON'S TYROSINE KINASE**FIELD OF THE INVENTION**

5 The present invention relates to compounds for inhibiting the activity of Bruton's tyrosine kinase and their use in manufacturing a medicament.

BACKGROUND OF THE INVENTION

Protein tyrosine kinase can catalyze a variety of substrate proteins tyrosine residues to phosphorylate, and plays an important role in modulating cell growth, proliferation and
10 differentiation. The aberrant kinase activity is associated with many human diseases, including cancer, autoimmune diseases and inflammatory diseases. As a mediator of cell signaling, protein tyrosine kinase can be a potential target of small molecule kinase inhibitors for modulating cell function, which is used for drug design.

Signaling through the B-cell receptor (BCR) controls a range of B-cell responses including
15 proliferation and differentiation into mature antibody producing cells. The BCR is a key regulatory point for B-cell activity and aberrant signaling can cause deregulated B-cell proliferation and formation of pathogenic autoantibodies that lead to multiple autoimmune and/or inflammatory diseases. Bruton's tyrosine kinase (BTK) is a member of the Tec tyrosine kinase family (Vetrie, D. et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of
20 proteintyrosine kinases. *Nature* **1993**, 361, 226–233.). BTK is expressed in most hematopoietic cells such as B cells, mast cells, and macrophages but not in T cells, natural killer cells, and plasma cells (Smith, C. I. et al. Expression of Bruton's agammaglobulinemia tyrosine kinase gene, BTK, is selectively down-regulated in T lymphocytes and plasma cells. *J. Immunol.* **1994**, 152, 557–565.) Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR)
25 stimulation to downstream intracellular responses.

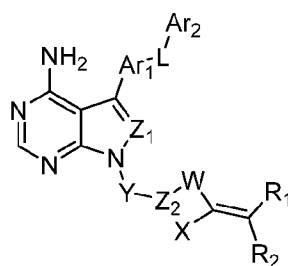
Btk is not only involved in the acquired immunity of the B lymphocyte-mediated signaling

pathway. 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 ϵ RI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B lineage lymphoid cells, and collagen-stimulated platelet aggregation. (Jeffries, C.A. et al. Bruton's Tyrosine Kinase Is a Toll/Interleukin-1 Receptor Domain-binding Protein That Participates in Nuclear Factor κ B Activation by Toll-like Receptor 4, *J.Biol. Chem.* **2003**, 278:26258-26264; Horwood, N. J. et al. Bruton's tyrosine kinase is required for lipopolysaccharide-induced tumor necrosis factor α production, *J. Exp. Med.* **2003**, 197:1603-1611; Iwaki, S. et al. Btk Plays a Crucial Role in the Amplification of FcRI-mediated Mast Cell Activation by Kit, *J.Biol. Chem.* **2005**, 280(48):40261-40270; Vassilev, A. et al. Bruton's Tyrosine Kinase as an Inhibitor of the Fas/CD95 Death-inducing Signaling Complex, *J.Biol. Chem.* **1999**, 274(3): 1646-1656; Quek, L.S. et al. A role for Bruton's tyrosine kinase (Btk) in platelet activation by collagen, *Curr. Biol.* **1998**, 8(20): 1137-1140). Lack of Btk has been shown to block BCR signaling and therefore inhibition of Btk could be a useful therapeutic approach to block B-cell mediated disease processes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds with Bruton's tyrosine kinase inhibitory activity.

The present invention described compounds comprising at least a compound of Formula (I), or pharmaceutically acceptable salts thereof.



Formula (I)

Wherein:

L is selected from CH₂, O, NR₃ or S(O)_x, wherein x is 0, 1 or 2;

Wherein R₃ is H, C₁-C₅ alkyl or substituted C₁-C₅ alkyl.

Ar₁, Ar₂ are independently selected from aryl, substituted aryl, heteroaryl or substituted heteroaryl;

Z₁ is selected from N or CR₄;

Wherein R₄ is selected from H, halogen, C₁-C₅ alkyl, substituted C₁-C₅ alkyl, C₁-C₈ heteroalkyl, substituted C₁-C₈ heteroalkyl, CN, C(O)(C₁-C₈ alkyl), and C(O)O(C₁-C₈ alkyl).

Y is selected from C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₁-C₈ heteroalkyl, substituted C₁-C₈ heteroalkyl, C₃-C₁₀ cycloalkyl, substituted C₃-C₁₀ cycloalkyl, C₂-C₁₀ heterocycloalkyl, substituted C₂-C₁₀ heterocycloalkyl, C₁-C₅alkyl(C₃-C₁₀)cycloalkyl and substituted C₁-C₅alkyl(C₃-C₁₀)cycloalkyl.

Z₂ is selected from N or CR₅;

Wherein R₅ is selected from H, halogen, C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₁-C₈ heteroalkyl, substituted C₁-C₈ heteroalkyl, and hydroxy.

W is selected from C₁-C₅ alkyl, substituted C₁-C₅ alkyl, C₁-C₅ heteroalkyl, substituted C₁-C₅ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O), C(O)N(R₆), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄ alkenyl.

Wherein R₆ is selected from H, C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl and substituted C₃-C₁₀ cycloalkyl; R₇ is selected from H, NH₂, NH(C₁-C₈ alkyl), and NH(C₃-C₇ cycloalkyl).

X is selected from C(O), OC(O), NR₈C(O), C(S), S(O)₂, OS(O)₂, NR₈S(O)₂;

Wherein R₈ is selected from H, C₁-C₅ alkyl or substituted C₁-C₅ alkyl.

R₁ and R₂ are independently selected from H, halogen, C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₁-C₈heteroalkyl, substituted C₁-C₈ heteroalkyl, C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, C₂-C₆ heterocycloalkyl, substituted C₂-C₆ heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C₁-C₄ alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₄ alkyl(C₃-C₇ cycloalkyl), C₁-C₄ alkyl(C₂-C₇ heterocycloalkyl).

For any and all of the embodiments, substituents can be selected from among from a subset of

the listed alternatives. For example, in some embodiments, Z_1 is N.

In some embodiments, L is O. In other embodiments, Z_1 is N, L is O.

In some embodiments, R_1 and R_2 are independently selected from H, methyl and $\text{CH}_2\text{N}(\text{CH}_3)_2$. In other embodiments, one of R_1 and R_2 is $\text{CH}_2\text{N}(\text{CH}_3)_2$, the other is H. In yet other embodiments,
5 R_1 and R_2 are each H.

In some embodiments, Z_1 is N; R_1 and R_2 are independently selected from H, methyl and $\text{CH}_2\text{N}(\text{CH}_3)_2$. In other embodiments, Z_1 is N; one of R_1 and R_2 is $\text{CH}_2\text{N}(\text{CH}_3)_2$, the other is H. In yet other embodiments, Z_1 is N; R_1 and R_2 are each H.

In some embodiments, Z_1 is N; L is O; R_1 and R_2 are independently selected from H, methyl
10 and $\text{CH}_2\text{N}(\text{CH}_3)_2$. In other embodiments, Z_1 is N; L is O; one of R_1 and R_2 is $\text{CH}_2\text{N}(\text{CH}_3)_2$, the other is H. In yet other embodiments, Z_1 is N; L is O; R_1 and R_2 are each H.

In some embodiments, Ar_1 and Ar_2 are aryl or substituted aryl. In other embodiments, Ar_1 is phenyl, Ar_2 is aryl or substituted aryl. In yet other embodiments, Ar_1 and Ar_2 are each phenyl.

In some embodiments, Z_1 is N; Ar_1 and Ar_2 are aryl or substituted aryl. In other embodiments,
15 Z_1 is N; Ar_1 is phenyl, Ar_2 is aryl or substituted aryl. In yet other embodiments, Z_1 is N; Ar_1 and Ar_2 are each phenyl.

In some embodiments, Z_1 is N; L is O; Ar_1 and Ar_2 are aryl or substituted aryl. In other embodiments, Z_1 is N; L is O; Ar_1 is phenyl, Ar_2 is aryl or substituted aryl. In yet other embodiments, Z_1 is N; L is O; Ar_1 and Ar_2 are each phenyl.

20 In some embodiments, Ar_1 is phenyl, Ar_2 is aryl or substituted aryl; R_1 and R_2 are independently selected from H, methyl and $\text{CH}_2\text{N}(\text{CH}_3)_2$. In other embodiments, Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $\text{CH}_2\text{N}(\text{CH}_3)_2$, the other is H. In yet other embodiments, Ar_1 and Ar_2 are each phenyl; R_1 and R_2 are each H.

In some embodiments, Z_1 is N; Ar_1 is phenyl, Ar_2 is aryl or substituted aryl; R_1 and R_2 are
25 independently selected from H, methyl and $\text{CH}_2\text{N}(\text{CH}_3)_2$. In other embodiments, Z_1 is N; Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $\text{CH}_2\text{N}(\text{CH}_3)_2$, the other is H. In yet other embodiments, Z_1 is N; Ar_1 and Ar_2 are each phenyl; R_1 and R_2 are each H.

In some embodiments, Z_1 is N; L is O; Ar_1 is each phenyl, Ar_2 is aryl or substituted aryl; R_1 and R_2 are independently selected from H, methyl and $CH_2N(CH_3)_2$. In other embodiments, Z_1 is N; L is O; Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H. In yet other embodiments, Z_1 is N; L is O; Ar_1 and Ar_2 are each phenyl; R_1 and R_2 are each H.

5 In some embodiments, Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N or CH; X is C(O), OC(O) or NC(O); W is C_1 - C_3 alkyl. In other embodiments, Z_1 is N; Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N or CH; X is C(O), OC(O) or NC(O); W is C_1 - C_3 alkyl. In yet other
10 other is H; Y is C_1 - C_3 alkyl; Z_2 is N or CH; X is C(O), OC(O) or NC(O); W is C_1 - C_3 alkyl.

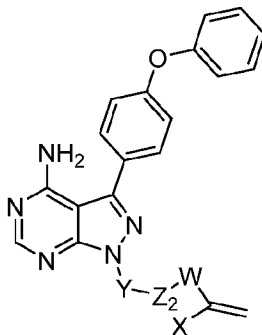
In some embodiments, Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N or CH; X is C(O) or NC(O); W is C_1 - C_3 alkyl. In other embodiments, Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_2 alkyl; Z_2 is CH; X is NC(O); W is C_1 - C_2 alkyl. In yet other embodiments, Ar_1 and Ar_2 are each phenyl; one of
15 R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N; X is C(O); W is C_2 - C_3 alkyl.

In some embodiments, Z_1 is N; Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N or CH; X is C(O) or NC(O); W is C_1 - C_3 alkyl. In other embodiments, Z_1 is N; Ar_1 and Ar_2 are phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_2 alkyl; Z_2 is CH; X is NC(O); W is C_1 - C_2 alkyl. In yet other embodiments, Z_1 is N; Ar_1 and Ar_2
20 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N; X is C(O); W is C_2 - C_3 alkyl.

In some embodiments, Z_1 is N; L is O; Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N or CH; X is C(O) or NC(O); W is C_1 - C_3 alkyl. In other embodiments, Z_1 is N; L is O; Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is
25 $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_2 alkyl; Z_2 is CH; X is NC(O); W is C_1 - C_2 alkyl. In yet other embodiments, Z_1 is N; L is O; Ar_1 and Ar_2 are each phenyl; one of R_1 and R_2 is $CH_2N(CH_3)_2$, the other is H; Y is C_1 - C_3 alkyl; Z_2 is N; X is C(O); W is C_2 - C_3 alkyl.

In a preferred embodiment of the present invention, the compound of Formula (I) or

pharmaceutically acceptable salt thereof is a compound of Formula (Ia),



Formula (Ia)

Wherein:

5 Y is selected from C₁-C₅ alkyl or substituted C₁-C₅ alkyl.

Z₂ is selected from N or CR₅;

Wherein R₅ is selected from H, halogen, C₁-C₃ alkyl, C₁-C₃ heteroalkyl, and hydroxy.

W is selected from C₁-C₅alkyl, substituted C₁-C₅alkyl, C₁-C₅ heteroalkyl, substituted C₁-C₅ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O), C(O)N(R₆), C(O)S, C(S)N(R₆),
 10 C(R₇)=N, and C₂-C₄alkenyl.

Wherein R₆ is selected from H, C₁-C₃alkyl, substituted C₁-C₃alkyl, C₃-C₆cycloalkyl and substituted C₃-C₆cycloalkyl; R₇ is selected from H, NH₂, NH(C₁-C₃ alkyl), and NH(C₃-C₆ cycloalkyl).

X is selected from C(O), OC(O), NR₈C(O), C(S), S(O)₂, OS(O)₂, NR₈S (O)₂;

15 Wherein R₈ is selected from H, C₁-C₃ alkyl, and substituted C₁-C₃ alkyl.

In some embodiments, X is selected from C(O), OC(O), NR₈C(O), C(S), S(O)₂, OS(O)₂, NR₈S (O)₂; Wherein R₈ is selected from H, methyl, ethyl, propyl and isopropyl. In other embodiments, X is selected from C(O), OC(O), NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl.

20 In some embodiments, W is selected from C₁-C₅ alkyl, substituted C₁-C₅ alkyl, C₁-C₅heteroalkyl, substituted C₁-C₅heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O),

C(O)N(R₆), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄alkenyl, and R₆ is selected from H, C₁-C₃alkyl, substituted C₁-C₃alkyl, C₃-C₆cycloalkyl, and substituted C₃-C₆cycloalkyl; R₇ is selected from H, NH₂, NH(C₁-C₃ alkyl), and NH(C₃-C₆ cycloalkyl). In other embodiments, W is selected from C₁-C₄ alkyl, C₁-C₃ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O), C(O)N(R₆), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄ alkenyl. And R₆ is selected from H, methyl and ethyl; R₇ is selected from H, NH₂ and NHCH₃. In yet other embodiments, W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.

In some embodiments, X is selected from C(O), OC(O), NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; W is selected from C₁-C₄ alkyl, C₁-C₃ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O), C(O)N(R₆), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄ alkenyl. And R₆ is selected from H, methyl and ethyl; R₇ is selected from H, NH₂ and NHCH₃. In other embodiments, X is selected from C(O), OC(O), NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.

In some embodiments, W is selected from C₁-C₄ alkyl, C₁-C₃ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), N(R₆)C(O), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄ alkenyl. And R₆ is selected from H, methyl and ethyl; R₇ is selected from H, NH₂ and NHCH₃. In yet other embodiments, W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl.

In some embodiments, X is selected from C(O), OC(O), NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; W is selected from C₁-C₄ alkyl, C₁-C₃ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), N(R₆)C(O), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄ alkenyl. And R₆ is selected from H, methyl and ethyl; R₇ is selected from H, NH₂ and NHCH₃. In other embodiments, X is selected from C(O), OC(O), NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl.

In some embodiments, Y is selected from C₁-C₅ alkyl or substituted C₁-C₅ alkyl. In other embodiments, Y is selected from C₁-C₃ alkyl.

In some embodiments, W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S; Y is selected from C₁-C₃ alkyl.

In some embodiments, W is selected from C₁-C₄ alkyl and C(O)(C₀-C₃)alkyl; Y is selected from C₁-C₃ alkyl.

In some embodiments, X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; Y is selected from C₁-C₃ alkyl.

5 In some embodiments, W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S; X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; Y is selected from C₁-C₃ alkyl.

In some embodiments, W is selected from C₁-C₄ alkyl and C(O)(C₀-C₃)alkyl; X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; Y
10 is selected from C₁-C₃ alkyl.

In some embodiments, Z₂ is selected from N and CH.

In some embodiments, Y is selected from C₁-C₃ alkyl; Z₂ is selected from N and CH.

In some embodiments, W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S; Z₂ is selected from N and CH. In other embodiments, W is selected from C₁-C₄ alkyl,
15 C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S; Z₂ is selected from N and CH; Y is selected from C₁-C₃ alkyl.

In some embodiments, W is selected from C₁-C₄ alkyl and C(O)(C₀-C₃)alkyl; Z₂ is selected from N and CH. In other embodiments, W is selected from C₁-C₄ alkyl and C(O)(C₀-C₃)alkyl; Z₂ is selected from N and CH; Y is selected from C₁-C₃ alkyl.

20 In some embodiments, X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; Z₂ is selected from N and CH. In other embodiments, In some embodiments, X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; Y is selected from C₁-C₃ alkyl, Z₂ is selected from N and CH.

In some embodiments, W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃)
25 and C(O)S; X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl; Z₂ is selected from N and CH. In other embodiments, W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S; X is selected from C(O),

OC(O), and $\text{NR}_8\text{C}(\text{O})$, and R_8 is selected from H, methyl, ethyl, propyl and isopropyl; Y is selected from $\text{C}_1\text{-C}_3$ alkyl; Z_2 is selected from N and CH.

In some embodiments, W is selected from $\text{C}_1\text{-C}_4$ alkyl and $\text{C}(\text{O})(\text{C}_0\text{-C}_3)\text{alkyl}$; X is selected from C(O), OC(O), and $\text{NR}_8\text{C}(\text{O})$, and R_8 is selected from H, methyl, ethyl, propyl and isopropyl;
 5 Z_2 is selected from N and CH. In other embodiments, W is selected from $\text{C}_1\text{-C}_4$ alkyl and $\text{C}(\text{O})(\text{C}_0\text{-C}_3)\text{alkyl}$; X is selected from C(O), OC(O), and $\text{NR}_8\text{C}(\text{O})$, and R_8 is selected from H, methyl, ethyl, propyl and isopropyl; Y is selected from $\text{C}_1\text{-C}_3$ alkyl; Z_2 is selected from N and CH.

In yet other embodiments, Y is selected from $\text{C}_1\text{-C}_2$ alkyl; Z_2 is CH; X is selected from OC(O) and $\text{NR}_8\text{C}(\text{O})$, and R_8 is selected from H, methyl, ethyl; W is selected from $\text{C}_1\text{-C}_3$ alkyl.

10 In yet other embodiments, Y is selected from $\text{C}_2\text{-C}_3$ alkyl; Z_2 is N; X is C(O); W is selected from $\text{C}_1\text{-C}_4$ alkyl, $\text{C}(\text{O})(\text{C}_0\text{-C}_3)\text{alkyl}$, $\text{C}(\text{O})\text{O}$, $\text{C}(\text{O})\text{N}(\text{CH}_3)$ and $\text{C}(\text{O})\text{S}$.

In yet other embodiments, Y is selected from $\text{C}_1\text{-C}_2$ alkyl; Z_2 is CH; X is selected from $\text{NR}_8\text{C}(\text{O})$, and R_8 is selected from H, methyl, ethyl; W is selected from $\text{C}_1\text{-C}_2$ alkyl.

In yet other embodiments, Y is selected from $\text{C}_2\text{-C}_3$ alkyl; Z_2 is N; X is C(O); W is selected
 15 from $\text{C}_2\text{-C}_4$ alkyl.

In yet other embodiments, Y is selected from $\text{C}_2\text{-C}_3$ alkyl; Z_2 is N; X is C(O); W is selected from $\text{C}(\text{O})(\text{C}_1\text{-C}_3)\text{alkyl}$.

In yet other embodiments, Y is selected from $\text{C}_2\text{-C}_3$ alkyl; Z_2 is N or CH; X is selected from $\text{NCH}_3\text{C}(\text{O})$ and OC(O); W is selected from CH_2 and C(O).

20 Most preferably, the compound or pharmaceutically acceptable salt thereof of the present invention is selected from any one of the following:

(S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-methylenepyrrolidin-2-one

(R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-
 25 methylenepyrrolidin-2-one

(S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-

methylenepiperidin-2-one

(R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene dihydrofuran-2(3H)-one

(S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene dihydrofuran-2(3H)-one

5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenedihydrofuran-2(3H)-one

(R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene pyrrolidin-2-one

5-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrrolidin-2-one

(S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene piperidin-2-one

(S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenetetrahydro-2H-pyran-2-one

1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrrolidin-2-one

1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepiperidin-2-one

1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-methylenepiperidin-2-one

1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrrolidine-2,5-dione

1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepiperidine-2,6-dione

3-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1-methyl-5-meth

yleneimidazolidine-2,4-dione

3-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-5-methylenethiazolidine-2,4-dione

(S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-(dimethylamino)ethylidene)dihydrofuran-2(3H)-one

(*S,E*)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-(dimethylamino)ethylidene)pyrrolidin-2-one

(*E*)-1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-(2-(dimethylamino)ethylidene)pyrrolidin-2-one

10 Any one of compounds of the present invention has a Btk activation IC₅₀ value of 10 μM or less. With particularly, the compounds of the the present invention has a Btk activation IC₅₀ value of 1 μM or less.

The present invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more of compounds of formula (I), and at least one pharmaceutically acceptable excipient, adjuvant or carrier.

The present invention provides the use of the pharmaceutical composition in manufacturing a medicament.

The present invention provides a method of modulating function of Btk receptor in animals or humans comprising a therapeutically effective amount of by administering to the subject a therapeutically effective amount of one or more of compounds of formula (I) or pharmaceutically acceptable salts thereof.

The present invention compounds or the pharmaceutical composition can be used in manufacturing a medicament of modulating function of Btk receptor in animals or humans.

The present invention compounds or the pharmaceutical composition can be used in manufacturing a medicament for the treatment of autoimmune diseases or conditions associated with aberrant B-cell proliferation such as rheumatoid arthritis, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions. Preferably applied in

manufacturing a medicament for lymphoma, myeloma or leukemia.

The present invention compounds or the pharmaceutical composition can be used in the treatment of autoimmune diseases or conditions associated with aberrant B-cell proliferation such as rheumatoid arthritis, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions. Wherein the autoimmune diseases associated with aberrant B-cell proliferation are preferably selected from lymphoma, myeloma or leukemia.

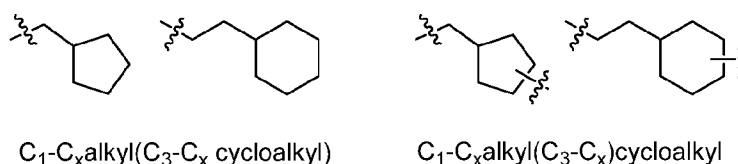
The present invention provides a method of treatment of autoimmune diseases or conditions associated with aberrant B-cell proliferation such as rheumatoid arthritis, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions, which comprising a therapeutically effective amount of one or more of compounds of formula (I) or pharmaceutically acceptable salts thereof. Wherein the autoimmune diseases associated with aberrant B-cell proliferation are preferably selected from lymphoma, myeloma or leukemia.

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings discussed below. Variables defined in this section, such as R, X, Z, Y and the like, are for reference within this section only, and are not meant to have the same meaning as may be used outside of this definitions section. Further, many of the groups defined herein can be optionally substituted. The listing in this definitions section of typical substituents is exemplary and is not intended to limit the substituents defined elsewhere within this specification and claims.

As used herein, C₁-C_x includes C₁-C₂, C₁-C₃... C₁-C_x.

The "()" used in a group with different position has different meanings. For example, C(O)(C₁-C_x)alkyl refers to -C(O)CH₂-, -C(O)CH₂CH₂-, etc. And C(O)(C₁-C₃alkyl) refers to acetyl, propionyl, etc. "C₁-C_xalkyl(C₃-C_x)cycloalkyl" and "C₁-C_xalkyl(C₃-C_x cycloalkyl)" also refer to different definitions. Illustrative examples are derived from, but not limited to, the following:

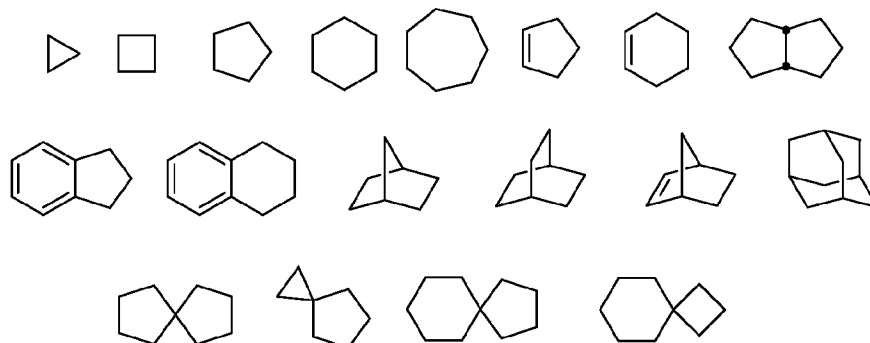


"Alkyl" refers to a saturated aliphatic hydrocarbon radical or linker including straight chain and branched chain groups of 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, more preferably 1 to 8 carbon atoms, or 1 to 6 carbon atoms, or 1 to 4 carbon atoms. "Lower alkyl" refers specifically to an alkyl group with 1 to 4 carbon atoms. Examples of alkyl groups include $-(CH_2)_3-$, methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and the like. Alkyl may be substituted or unsubstituted. Typical substituent groups include cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, C-carboxy, O-carboxy, nitro, silyl, amino and $-NR^xR^y$, where R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring.

"heteroalkyl" include optionally substituted alkyl radicals in which one or more skeletal chain atoms is a heteroatom, e.g., oxygen, nitrogen, sulfur, silicon, phosphorus or combinations thereof. The heteroatom(s) may be placed at any interior position of the heteroalkyl group or at the position at which the heteroalkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_3$, $-OCH_2-$, $-CH_2-NH-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-N(CH_3)-CH_3$, $-NCH_2CH_2-$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$. In addition, up to two heteroatoms may be consecutive, such as, by way of example, $-CH_2-NH-OCH_3$.

"Cycloalkyl" refers to a 3 to 8 member all-carbon monocyclic ring, an all-carbon 5-member/6-member or 6-member/6-member fused bicyclic ring, or a multicyclic fused ring (a "fused" ring system means that each ring in the system shares at least an adjacent carbon atom with each other ring in the system) group wherein one or more of the rings may contain one or more double bonds but none of the rings has a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, adamantane, cycloheptane, cycloheptatriene, and the like. A cycloalkyl group may be substituted or unsubstituted. Typical substituent groups include alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, O-carbamyl, N-carbamyl, Camido, N-amido, nitro,

amino and $-NR^xR^y$, with R^x and R^y as defined above. Illustrative examples of cycloalkyl are derived from, but not limited to, the following:



"Cycloalkylalkyl" or "Alkylcycloalkyl" means an alkyl radical, as defined herein, substituted with a cycloalkyl group. Non-limiting cycloalkylalkyl or alkylcycloalkyl groups include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, methylcyclobutyl and the like.

"Alkenyl" refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like.

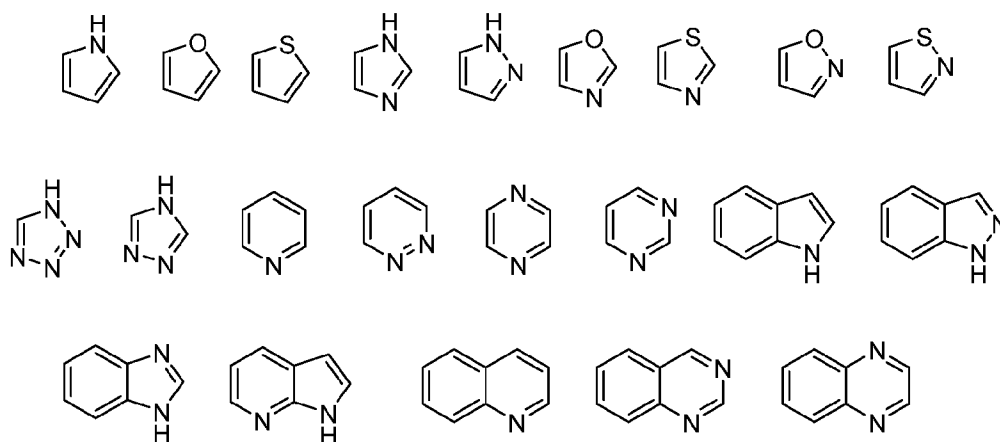
"Aryl" refers to an all-carbon monocyclic or fused-ring polycyclic groups of 6 to 12 carbon atoms having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. Typical substituents include halo, trihalomethyl, alkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, nitro, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, Ocarbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, sulfinyl, sulfonyl, amino and $-NR^xR^y$, with R^x and R^y as defined above.

"Heteroaryl" refers to a monocyclic or fused ring group of 5 to 12 ring atoms containing one, two, three or four ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, and, in addition, having a completely conjugated π -electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine, tetrazole, triazine, and carbazole. The heteroaryl group may be substituted or unsubstituted. Typical substituents include alkyl,

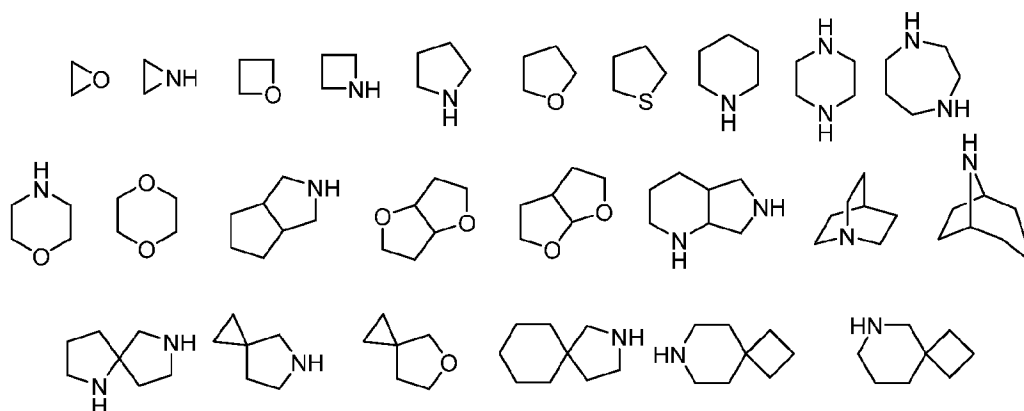
cycloalkyl, halo, trihalomethyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, nitro, carbonyl, thiocarbonyl, sulfonamido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, amino and $-NR^xR^y$ with R^x and R^y as defined above.

- 5 A pharmaceutically acceptable heteroaryl is one that is sufficiently stable to be attached to a compound of the invention, formulated into a pharmaceutical composition and subsequently administered to a patient in need thereof.

Examples of typical monocyclic heteroaryl groups include, but are not limited to:



- 10 "Heteroalicyclic" or "heterocycle" refers to a monocyclic, fused ring group or spiro having in the ring(s) of 3 to 12 ring atoms, in which one or two ring atoms are heteroatoms selected from N, O, and $S(O)_n$ (wherein n is 0, 1 or 2), the remaining ring atoms being C. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated π -electron system. Examples of suitable saturated heteroalicyclic groups include, but are not limited to:



The heterocycle group is optionally substituted with one or two substituents independently selected from halo, lower alkyl, lower alkyl substituted with carboxy, ester hydroxy, or mono or dialkylamino.

"Hydroxy" refers to an -OH group.

5 "Alkoxy" refers to both an -O-(alkyl) or an -O-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Haloalkoxy" refers to an -O-(haloalkyl) group. Representative examples include, but are not limited to, trifluoromethoxy, tribromomethoxy, and the like.

10 "Aryloxy" refers to an -O-aryl or an -O-heteroaryl group, as defined herein. Representative examples include,

but are not limited to, phenoxy, pyridinyloxy, furanyloxy, thienyloxy, pyrimidinyloxy, pyrazinyloxy, and the like, and derivatives thereof.

"Mercapto" refers to an -SH group.

15 "Alkylthio" refers to an -S-(alkyl) or an -S-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, methylthio, ethylthio, propylthio, butylthio, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, and the like.

"Arylthio" refers to an -S-aryl or an -S-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenylthio, pyridinylthio, furanylthio, thienylthio, 20 pyrimidinylthio, and the like and derivatives thereof.

"Acyl" or "carbonyl" refers to a -C(O)R" group, where R" is selected from the group consisting of hydrogen, lower alkyl, trihalomethyl, unsubstituted cycloalkyl, aryl optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of lower alkyl, trihalomethyl, lower alkoxy, halo and -NR^xR^y groups, heteroaryl (bonded through a ring carbon) optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of lower alkyl, trihaloalkyl, lower alkoxy, halo and -NR^xR^y groups and 25 heteroalicyclic (bonded through a ring carbon) optionally substituted with one or more, preferably

one, two, or three substituents selected from the group consisting of lower alkyl, trihaloalkyl, lower alkoxy, halo and $-NR^xR^y$ groups. Representative acyl groups include, but are not limited to, acetyl, trifluoroacetyl, benzoyl, and the like.

"Aldehyde" refers to an acyl group in which R" is hydrogen.

5 "Thioacyl" or "thiocarbonyl" refers to a $-C(S)R''$ group, with R" as defined above.

A "thiocarbonyl" group refers to a $-C(S)R''$ group, with R" as defined above.

A "C-carboxy" group refers to a $-C(O)OR''$ group, with R" as defined above.

An "O-carboxy" group refers to a $-OC(O)R''$ group, with R" as defined above.

10 "Ester" refers to a $-C(O)OR''$ group with R" as defined herein except that R" cannot be hydrogen.

"Acetyl" group refers to a $-C(O)CH_3$ group.

"Halo" group refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

"Trihalomethyl" group refers to a methyl group having three halo substituents, such as a trifluoromethyl group.

15 "Cyano" refers to a $-C\equiv N$ group.

A "sulfinyl" group refers to a $-S(O)R''$ group wherein, in addition to being as defined above, R" may also be a hydroxy group.

A "sulfonyl" group refers to a $-S(O)_2R''$ group wherein, in addition to being as defined above, R" may also be a hydroxy group.

20 "S-sulfonamido" refers to a $-S(O)_2NR^xR^y$ group, with R^x and R^y as defined above.

"N-sulfonamido" refers to a $-NR^xS(O)_2R^y$ group, with R^x and R^y as defined above.

"O-carbamyl" group refers to a $-OC(O)NR^xR^y$ group with R^x and R^y as defined above.

"N-carbamyl" refers to an $R^yOC(O)NR^x-$ group, with R^x and R^y as defined above.

"O-thiocarbamyl" refers to a $-OC(S)NR^xR^y$ group with R^x and R^y as defined above.

"N-thiocarbamyl" refers to a $R^yOC(S)NR^x$ - group, with R^y and R^x as defined above.

"Amino" refers to an $-NR^xR^y$ group, wherein R^x and R^y are both hydrogen.

"C-amido" refers to a $-C(O)NR^xR^y$ group with R^x and R^y as defined above.

"N-amido" refers to a $R^xC(O)NR^y$ group, with R^x and R^y as defined above.

5 "Nitro" refers to a $-NO_2$ group.

"imine" refers to a $-N=C$ - group.

"Haloalkyl" means an alkyl, preferably lower alkyl, that is substituted with one or more same or different halo atoms, e.g., $-CH_2Cl$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$, and the like.

10 "Hydroxyalkyl" means an alkyl, preferably lower alkyl, that is substituted with one, two, or three hydroxy groups; e.g., hydroxymethyl, 1 or 2-hydroxyethyl, 1,2-, 1,3-, or 2,3-dihydroxypropyl, and the like.

"Aralkyl" means alkyl, preferably lower alkyl, that is substituted with an aryl group as defined above; e.g., $-CH_2phenyl$, $-(CH_2)_2phenyl$, $-(CH_2)_3phenyl$, $CH_3CH(CH_3)CH_2phenyl$, and the like and derivatives thereof.

15 "Heteroaralkyl" group means alkyl, preferably lower alkyl, that is substituted with a heteroaryl group; e.g., $-CH_2pyridinyl$, $-(CH_2)_2pyrimidinyl$, $-(CH_2)_3imidazolyl$, and the like, and derivatives thereof.

"Monoalkylamino" means a radical $-NHR$ where R is an alkyl or unsubstituted cycloalkyl group; e.g., methylamino, (1-methylethyl)amino, cyclohexylamino, and the like.

20 "Dialkylamino" means a radical $-NRR$ where each R is independently an alkyl or unsubstituted cycloalkyl group; dimethylamino, diethylamino, (1-methylethyl)-ethylamino, cyclohexylmethylamino, cyclopentylmethylamino, and the like.

The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from among oxygen, sulfur, nitrogen, silicon and phosphorus, but
25 are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms can all be the same as one another, or some or all of the two or more

heteroatoms can each be different from the others.

The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, 5 alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, acyl, nitro, haloalkyl, fluoroalkyl, amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance 10 occurs and instances in which it does not. For example, "heterocycle group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycle group is substituted with an alkyl group and situations where the heterocycle group is not substituted with the alkyl group.

The term "acceptable" or "pharmaceutically acceptable", with respect to a formulation, 15 composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated or does not abrogate the biological activity or properties of the compound, and is relatively nontoxic.

"Therapeutically effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease 20 or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The "therapeutically effective amount" can vary depending on the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be readily apparent to those skilled in the 25 art or capable of determination by routine experimentation.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts include:

(1) acid addition salts, which can be obtained by reaction of the free base of the parent

compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

As used herein, when any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. The compounds of the present disclosure may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers or diastereomers. Accordingly, any chemical structures within the scope of the specification depicted, in whole or in part, with a relative configuration encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into the component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan.

Compounds of Formula I include, but are not limited to optical isomers of compounds of Formula I, racemates, and other mixtures thereof. In those situations, the single enantiomers or diastereomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. In addition, compounds of Formula I include Z- and E- forms (or cis- and trans- forms) of compounds with double bonds. Where compounds of Formula I exist in various tautomeric forms, chemical entities of the present invention include all tautomeric forms of the compound.

Compounds of the present disclosure include, but are not limited to compounds of Formula I, and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, solvates, crystal forms (including polymorphs and clathrates), chelates, non-covalent complexes, prodrugs, and mixtures thereof. In certain embodiments, the compounds described herein are in the form of pharmaceutically acceptable salts. As used henceforth, the term "compound" encompasses not only the compound itself, but also a pharmaceutically acceptable salt thereof, a solvate thereof, a chelate thereof, a non-covalent complex thereof, a prodrug thereof, and mixtures of any of the foregoing.

As noted above, prodrugs also fall within the scope of chemical entities, for example, ester or amide derivatives of the compounds of Formula I, I(a). The term "prodrugs" includes any compounds that become compounds of Formula I, I(a) when administered to a patient, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula I.

The present invention compounds can be in the form of composition by oral, inhalation, rectal or parenteral administration administered to patients in need of such treatment. For oral administration, the compound/pharmaceutical composition is a solid dosage form such as tablets, powders, granules, capsules, etc., or a liquid dosage form such as aqueous agents, oil-based suspension, syrup, and elixir agents. For parenteral administration, the compound/pharmaceutical composition is a solution for injection, an aqueous agent, or an oil-based suspension. Preferably, the dosage form is tablets, coated tablets, capsules, suppositories, nasal sprays and injections, and more preferably, is a formulation released at a specific site of intestine.

The dosage forms of the compound and pharmaceutically composition disclosed in the invention can be prepared by the conventional methods in pharmaceutical industry. For example, the active ingredient is mixed with one or more excipients, and then formed into the desired dosage form.

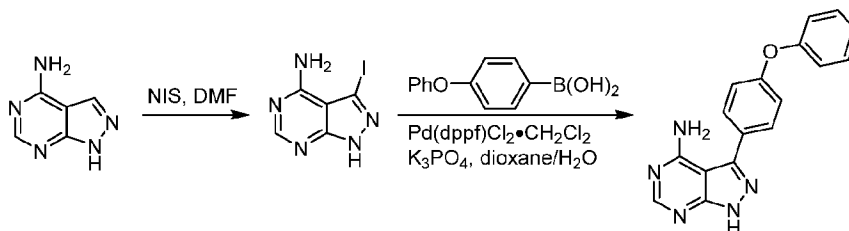
EXAMPLES

The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula (I) of the present invention.

The following examples are only used to disclose the preferred embodiments of the present invention, to help technicians in the art understand well, but are not used to limit the spirit and scope of the present invention. In the examples of the present invention, the approach or methods or the like is conventional in the art without specification. The compounds of the present invention can be prepared through, but not limited to, one or more of the following general reaction scheme:

Example 1:

10 Synthesis of 3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

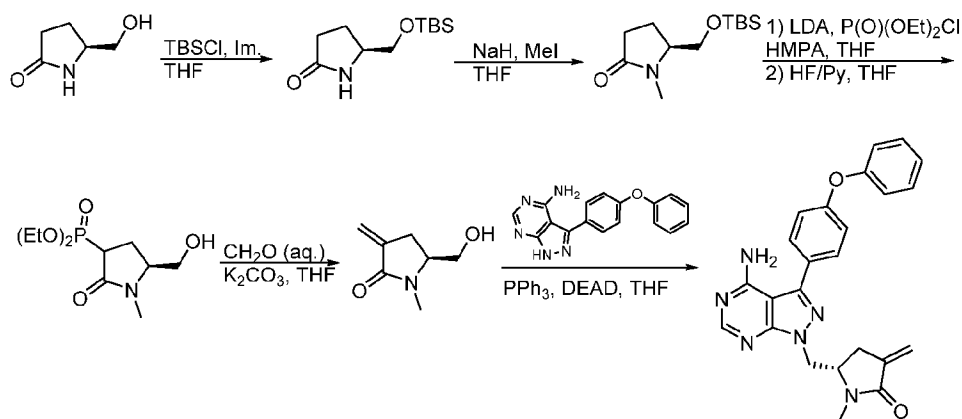


Step 1: To the solution of 3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.4 g, 40.0 mmol) in DMF (100 mL) was added NIS (10.8 g, 48.0 mmol). The resulting mixture was then heated to 70°C and stirred for 16 h. Poured into ice water, the solid was collected by filtration, and washed with saturated aqueous Na₂CO₃ solution and water. After drying, the desired product was obtained as yellow solid (9.3 g, 77%).

Step 2: To a stirred suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (9.0 g, 34.5 mmol) and (4-phenoxyphenyl)boronic acid (9.6 g, 45.0 mmol) in degassed dioxane (200 mL) was added a solution of K₃PO₄ (21.9 g, 103.5 mmol) in water (50 mL). The mixture was flushed with nitrogen, then added Pd(dppf)₂Cl₂•CH₂Cl₂ (5.6 g, 6.9 mmol), and degassed again. The resulting mixture was heated at 90°C for 36 h and then allowed to cool to room temperature. The reaction mixture was poured into ice water and the solid was collected by filtration, washed with water and EtOH each for twice. The crude product was purified by recrystallization in EtOAc to give gray solid (7.0 g, 67%). LC-MS[M+H]⁺-m/z 304.

Example 2:

Synthesis of (S)-5-(((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-methylenepyrrolidin-2-one



- 5 Step 1: To the mixture of (S)-5-(hydroxymethyl)pyrrolidin-2-one (6.0 g, 46.5 mmol) and imidazole (6.3 g, 93.0 mmol) in THF (180 mL) was added t-Butyldimethylsilyl chloride (6.3 g, 48.8 mmol) in portions at 0°C. The resulting suspension was stirred at room temperature for overnight. The mixture was poured into saturated NH₄Cl (aq.) solution and extracted with EtOAc. The combined organic solution was dried over anhydrous Na₂SO₄, filtered, and concentrated in
- 10 vacuo. The residue was purified by column chromatography (PE/EA = 4:1) to give the desired product as a yellow oil (7.1 g, 66%).

- Step 2: To the solution of (S)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one in THF (40 mL) at 0°C was carefully added NaH (60% in mineral oil, 0.66 g, 16.4 mmol), and stirred for 30 min. The suspension was then added MeI (4.7 mL, 76.4 mmol) and stirred at room temperature for
- 15 4h. The reaction was stopped by added saturated NH₄Cl (aq.) solution and extracted with EtOAc. The combined organic solution was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography (PE/EA = 4:1) to give the desired product as a yellow oil (2.4 g, 90%).

- Step 3: To the solution of (S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-methylpyrrolidin-2-one
- 20 (1.0 g, 4.1 mmol) in THF (30 mL) at -50°C under N₂ was added LDA (1.5 M in THF, 5.5 mL, 8.2 mmol). Then warmed to 0°C over 45 min, and added Diethyl chlorophosphate (0.74 g, 4.1 mmol). The resulting mixture was stirred at 15 °C for overnight. The reaction was stopped by added 1N

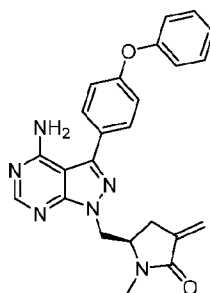
HCl (aq.), and the mixture was extracted with EtOAc. The combined organic solution was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was redissolved in (30 mL), cooled to -20°C, added Olah's Reagent (70%, 2.0 mL), and stirred at room temperature for 3h. The mixture was added water and extracted with EtOAc for several times. The combined organic solution was dried and concentrated in vacuo. The residue was purified by column chromatography (EA) to give the desired product as a colorless oil (70 mg, 6%).

Step 4: To the solution of diethyl ((5S)-5-(hydroxymethyl)-1-methyl-2-oxopyrrolidin-3-yl)-phosphonate (70mg, 0.26 mmol) in THF (10 mL) was added formaldehyde (37%, 0.15 mL) and solution of K₂CO₃ (54mg, 0.39mmol) in water (2.0 mL) dropwise. The resulting mixture was stirred for 3h, added silica gel and concentrated in vacuo. The residue was purified by column chromatography to give the desired product as a colorless oil (31 mg, 84%).

Step 5: To the suspension of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (67 mg, 0.22 mmol), (S)-5-(hydroxymethyl)-1-methyl-3-methylenepyrrolidin-2-one (31mg, 0.22 mmol) and triphenylphosphine (173 mg, 0.66 mmol) in dry THF (25 mL) at -25 °C was added a solution of DEAD (115 mg, 0.66 mmol) in THF (0.5 mL) dropwise. The resulting mixture was stirred at -25 °C for 1h, then warmed to room temperature and stirred for overnight. The reaction mixture was concentrated in vacuo and purified column chromatography (DCM/CH₃OH = 100:1→50:1) to give a crude product which was further purified by PTLC (EA), and recrystallization from ether. The desired product was obtained as light yellow solid (25 mg, 27%). LC-MS[M+H]⁺-m/z 427.

Example 3:

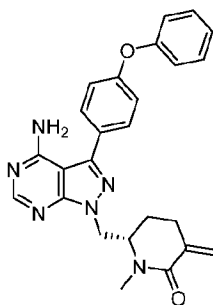
Synthesis of (R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-methylenepyrrolidin-2-one



Similar procedure to the example 2 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 427

Example 4

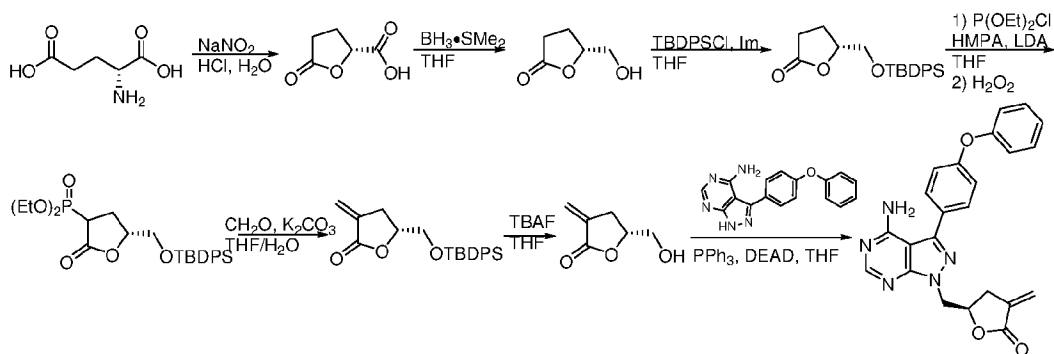
Synthesis of (S)-6-(((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-methylenepiperidin-2-one



- 5 Similar procedure to the example 2 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 441.

Example 5

Synthesis of (R)-5-(((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenedihydrofuran-2(3H)-one



10

Step 1: To a solution of D-glutamic acid (10.07 g, 68.4 mmol) in 20 ml of concd. HCl and 40 mL water was added a solution of NaNO₂ (7.0 g, 101.5 mmol) in water (20 mL) slowly at -5° C. The mixture was continued to stir for overnight at room temperature. The reaction mixture was evaporated in vacuo below 50° C to give yellow oil, which was dissolved in EtOAc. The solid
15 formed was filtered and washed with EtOAc. The filtrate and washing solution were combined, dried over Na₂SO₄ and concentrated in vacuo. The crude product was used directly in the next step without further purification.

Step 2: To the solution of (R)-5-oxotetrahydrofuran-2-carboxylic acid (7.2 g, 55.2 mmol) in

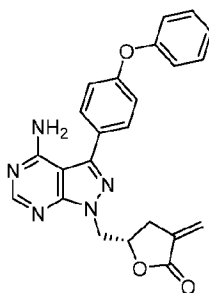
THF (100 mL) at room temperature was added $\text{BH}_3 \cdot \text{SMe}_2$ (10 M, 6.6 mL). The resulting mixture was continued to stirred for 4h, then added 25 mL MeOH and concentrated in vacuo. The residue was used directly in the next step without further purification.

Step 3: To the mixture of (R)-5-(hydroxymethyl)tetrahydrofuran-2(3H)-one (5.8 g, 50.0 mmol) and imidazole (6.8 g, 100.0 mmol) in THF (200 mL) at 0°C was added tert-Butyldiphenylchlorosilane (14.4 g, 52.5 mmol) in portions. The resulting suspension was stirred at room temperature for overnight. The mixture was poured into saturated NH_4Cl (aq.) solution and extracted with EtOAc. The combined organic solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography (PE/EA = 4:1) to give the desired product as a white solid (9.5 g, 54%).

Similar procedure of step 4~7 to the example 2 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 414.

Example 6

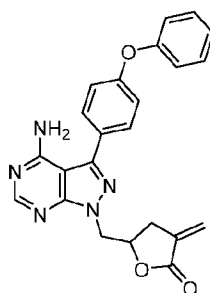
Synthesis of (S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenetetrahydrofuran-2(3H)-one



Similar procedure to the example 5 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 414.

Example 7

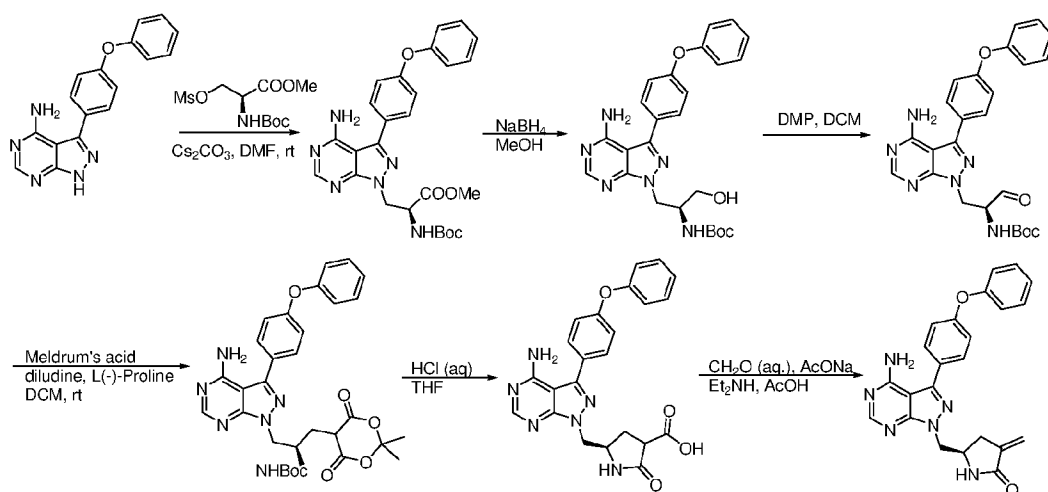
Synthesis of 5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenetetrahydrofuran-2(3H)-one



Similar procedure to the example 5 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 414.

Example 8

- 5 Synthesis of (R)-5-(((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenepyrrolidin-2-one



- Step 1: To the solution of N-(tert-Butoxycarbonyl)-L-serine (4.38 g, 20.0 mmol) and TEA (6.7 mL, 48.0 mmol) in DCM (50 mL) at 0°C was added MsCl (1.9 mL, 24.8 mmol) dropwise. Diluted with DCM, and washed with water for twice. The organic phase was dried and concentrated.

- To a 100 mL flask was added 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (4.04 g, 13.3 mmol), Cs₂CO₃ (5.22 g, 16.0 mmol) and DMF (50 mL). The mixture was stirred for 10 min, and then added the above methanesulfonate in DMF (5 mL). The resulting mixture was stirred at room temperature for overnight. Poured into brine, and extracted with EtOAc. The combined organic solution was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was used directly in the next step without further purification. LC-MS[M+H]⁺-m/z 505.

Step 2: To the solution of methyl (S)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)-2-((tert-butoxycarbonyl)amino)propanoate (6.3 g, 12.5 mmol) in MeOH (50 mL) was added NaBH₄ (2.4 g, 62.5 mmol) in portions. The mixture was stirred for overnight. Concentrated in vacuo and purified by column chromatography (PE/EA=1:1→EA) to give a white solid (3.1 g, 49% for two steps). LC-MS[M+H]⁺-m/z 477.

Step 3: To the solution of tert-butyl (S)-(1-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)-3-hydroxypropan-2-yl)carbamate (3.1 g, 6.5 mmol) in DCM (100 mL) was added Dess-Martin periodinane (DMP) (5.5 g, 13.0 mmol). The resulting suspension was stirred for overnight. Filtered and the filtrate was concentrated in vacuo and purified by column chromatography (DCM/MeOH = 30:1) to give the desired product as yellow solid (1.2 g, 38%). LC-MS[M+H]⁺-m/z 475.

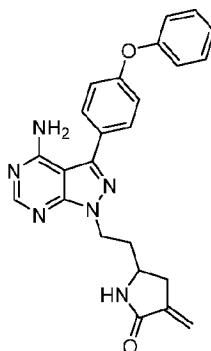
Step 4: To the solution of tert-butyl (S)-(1-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)-3-oxopropan-2-yl)carbamate (1.2 g, 2.5 mmol) in MeCN (20 mL) at room temperature was added Meldrum's acid (360 mg, 2.5 mmol), Diludine (633 mg, 2.5 mmol) and L(-)-Proline (29 mg, 0.25 mmol). The reaction mixture was turned cleared after stirring for 3h at rt. Concentrated in vacuo and purified by column chromatography to give the desired product as white solid (1.41 g, 92%). LC-MS[M+H]⁺-m/z 603.

Step 5: To the solution of the above product (1.41 g, 2.3 mmol) in THF (20 mL) was added conc. HCl (2 mL). The mixture was stirred for overnight. Added water and extracted with EtOAc. The combined organic solution was dried and concentrated in vacuo. The crude product was used directly in the next step. LC-MS[M+H]⁺-m/z 445.

Step 6: A mixture of (5R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-2-oxopyrrolidine-3-carboxylic acid (933 mg, 2.1 mmol), acetic acid (15 mL), sodium acetate trihydrate (644 mg, 4.7 mmol), diethylamine (3.8 mL), and 37% formalin (11.5 mL) was refluxed for 2h. Then the mixture was cooled, poured into water, and extracted with EtOAc. The combined extracts were washed successively with diluted hydrochloric acid, a saturated NaHCO₃ aqueous solution, and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (DCM/MeOH = 30:1) to give the desired product as white solid (495 mg, 57%). LC-MS[M+H]⁺-m/z 413.

Example 9

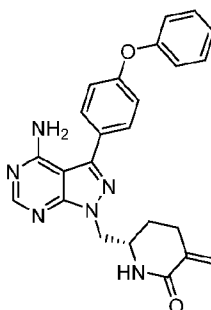
Synthesis of 5-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrrolidin-2-one



- 5 Similar procedure to the example 8 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 427.

Example 10

Synthesis of (S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenepiperidin-2-one



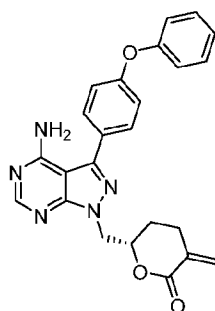
10

Similar procedure to the example 8 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 427.

Example 11

Synthesis of (S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenetetrahydro-2H-pyran-2-one

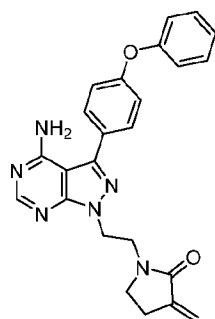
15



Similar procedure to the example 7 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 428.

Example 12

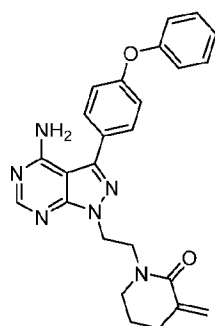
- 5 Synthesis of 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylpyrrolidin-2-one



Similar procedure to the example 7 was followed to arrive at the title compound with 1-(2-hydroxyethyl)pyrrolidin-2-one as the starting material, with the LC-MS[M+H]⁺-m/z 427.

10 Example 13

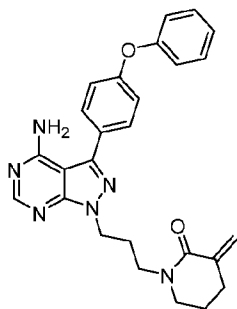
Synthesis of 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylpiperidin-2-one



Similar procedure to the example 2 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 441.

Example 14

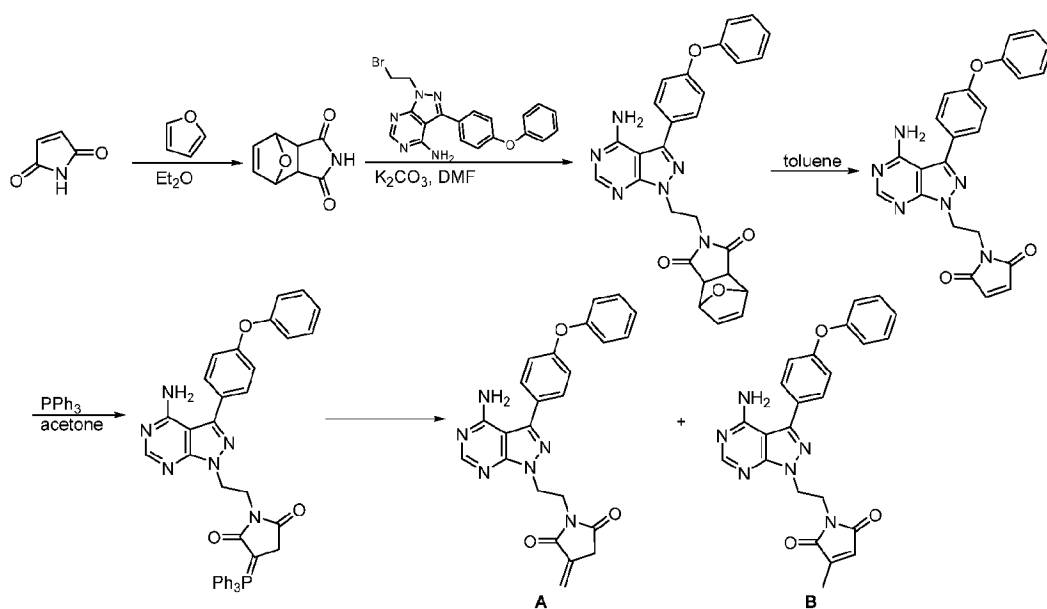
5 Synthesis of 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-methylenepiperidin-2-one



Similar procedure to the example 2 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 455.

Example 15

10 Synthesis of 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrrolidine-2,5-dione



Step 1: Maleimide (1.94 g, 20 mmol) and furan (2.04 mL, 30 mmol) were dissolved in ethyl

acetate (50 mL). The mixture was heated inside a 100 mL of autoclave bomb at 100 °C for overnight. The bomb was cooled down to room temperature, and the inside solid was rinsed with methanol, concentrated and crystallized in PE/EA. The product was collected by filtration to give the desired product as white solid (3.1 g, 95%).

5 Step 2: 1-(2-bromoethyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine: The suspension of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (6.6 g, 20 mmol) and K₂CO₃ (11.1 g, 80 mmol) in DMF (100 mL) was heated to 80°C, then added 1,2-Dibromoethane (8.7 mL, 100 mmol). The resulting mixture was continued to stir for 3h, then cooled to room temperature. Poured into water, and extracted with EtOAc. The combined organic extracts were
10 washed with brine and water, dried and concentrated in vacuo. The residue was purified by column chromatography (DCM/MeOH = 30:1) to give the desired product as yellow solid (7.5 g, 91%). LC-MS[M+H]⁺-m/z 410.

To the 100 mL flask was added 1-(2-bromoethyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-4-amine (1.23 g, 3.0 mmol), 3,6-oxo-Δ⁴-tetrahydrophthalimide (495 mg, 3.0 mmol),
15 K₂CO₃ (995 mg, 7.2 mmol) and DMF (15 mL). The resulting mixture was stirred at 80°C for overnight. The mixture was cooled, poured into water, and extracted with EtOAc. The extracts was washed with brine and water, dried and concentrated. The residue was purified by column chromatography to give the desired product as white solid (1.26 g, 85%). LC-MS[M+H]⁺-m/z 495.

Step 3: 2-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-
20 3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (1.26 g, 2.6 mmol) was dissolved in toluene (30 mL), and refluxed for overnight. The mixture was concentrated in vacuo and purified by column chromatography to give the desired product as white solid (897 mg, 81%). LC-MS[M+H]⁺-m/z 427.

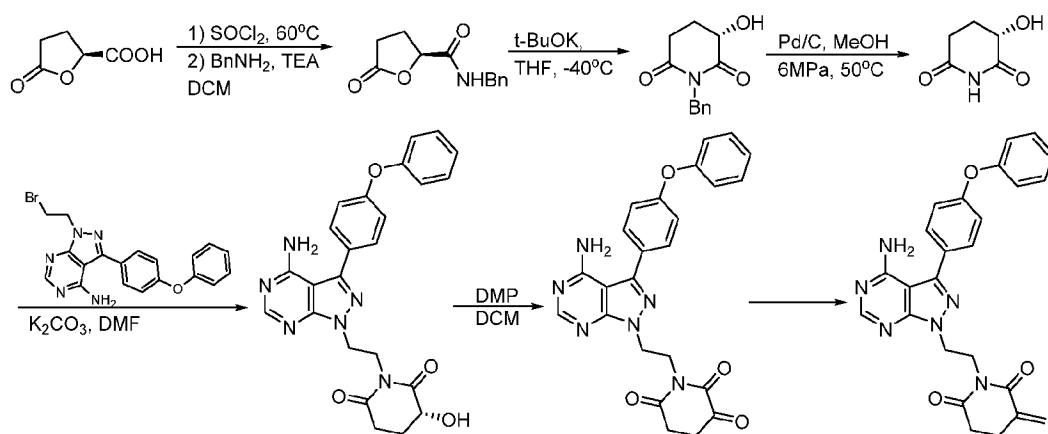
Step 4: To the mixture of 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1H-pyrrole-2,5-dione (852 mg, 2.0 mmol) in acetone (20 mL) was added PPh₃ (576 mg, 2.2 mmol). The mixture was refluxed for overnight, then concentrated in vacuo. The residue was purified by column chromatography to give the desired product as white solid (1.24 g, 90%).

Step 5: To the 50 mL flask was added 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-

pyrimidin-1-yl)ethyl)-3-(triphenyl-15-phosphanylidene)pyrrolidine-2,5-dione (344mg, 0.5 mmol), paraformaldehyde (60 mg, 1.0 mmol) and 1,2-Dichloroethane (30 mL). The mixture was refluxed for overnight, then concentrated in vacuo and purified by column chromatography (DCM/MeOH = 30:1) to give the desired product as a mixture of A and B (330 mg, 75%). LC-MS[M+H]⁺-m/z 441.

5 Example 16

Synthesis of 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepiperidine-2,6-dione



Step 1: To (S)-5-oxotetrahydrofuran-2-carboxylic acid (2.6 g, 20.0 mmol) at 0°C was carefully added SOCl₂ (10 mL). The mixture was stirred at 60°C for 4h, then cooled to room temperature, and concentrated in vacuo. The residue was redissolved in DCM (10 mL), cooled to 0°C, and added TEA (5.6 mL, 40 mmol), then slowly added benzylamine (2.14 g, 20 mmol) in DCM (20 mL) dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for overnight. The mixture was washed with water for twice, dried, concentrated in vacuo, and the residue was purified by column chromatography to give the desired product as white solid (3.7 g, 85%).

Step 2: To the mixture of (S)-N-benzyl-5-oxotetrahydrofuran-2-carboxamide (2.19 g, 10.0 mmol) in THF (50 mL) at -40°C was added t-BuOK (1.12 g, 10.0 mmol) under the protection of nitrogen. The mixture was continued to stir for 3h, then poured into saturated aqueous NH₄Cl, and extracted with EtOAc. The combined organic solution was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was used directly in the next step without further purification.

Step 3: The mixture of (S)-1-benzyl-3-hydroxypiperidine-2,6-dione (2.19 g, 10.0 mmol), 10% Pd/C (220 mg) and MeOH was reacted under 6 MPa hydrogen atmosphere at 50°C for 24h. The mixture was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The crude product was crystallized with PE/EA to give the desired product as white solid (0.96 g, 74%).

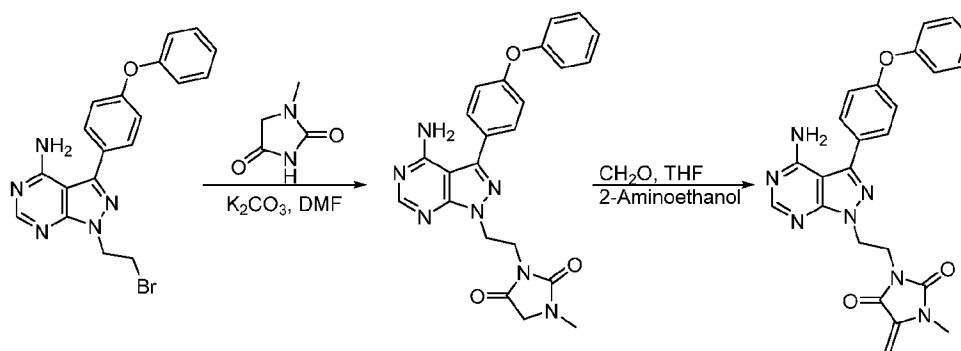
5 Step 4: The mixture of 1-(2-bromoethyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (820 mg, 2.0 mmol), (S)-3-hydroxypiperidine-2,6-dione (258 mg, 2.0 mmol), K₂CO₃ (663 mg, 4.8 mmol) and DMF (10 mL) was stirred at 80°C for overnight. Then cooled, poured into water, and extracted with EtOAc. The combined organic phase was washed with brine and water, dried and concentrated. The residue was purified by column chromatography to give the desired
10 product as white solid (642 mg, 70%). LC-MS[M+H]⁺-m/z 459.

Step 5: To the mixture of (R)-1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)ethyl)-3-hydroxypiperidine-2,6-dione (642 mg, 1.4 mmol) in DCM (30 mL) was added Dess-Martin periodinane (DMP) (1.19 g, 2.8 mmol). The resulting mixture was stirred for overnight. When the reaction was completed, the insolubles was filtered off, and the filtrate was
15 concentrated under reduced pressure. The residue was purified by column chromatography to give the desired product as light yellow solid (498 mg, 78%). LC-MS[M+H]⁺-m/z 457.

Step 6: To the suspension of Methyltriphenylphosphonium bromide (472 mg, 1.3 mmol) in dry THF (20 mL) at 0°C was added NaH (60% in mineral oil, 68 mg, 1.7 mmol). The mixture was stirred at room temperature for 0.5 h, then added 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo-
20 [3,4-d]pyrimidin-1-yl)ethyl)piperidine-2,3,6-trione (498 mg, 1.1 mmol). The resulting mixture was stirred at room temperature for overnight. Added one drop of water to stop the reaction, the mixture was poured into brine and extracted with EtOAc. The combined organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was firstly purified by column chromatography (DCM/MeOH = 30:1), then refined through PTLC and recrystallization
25 from ether to give the desired product as white solid (325 mg, 65%). LC-MS[M+H]⁺-m/z 455.

Example 17

Synthesis of 3-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1-methyl-5-methyleneimidazolidine-2,4-dione

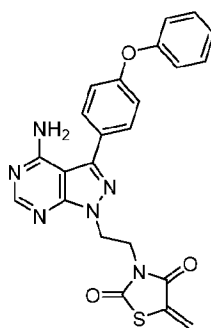


Step 1: To the suspension of 1-methylimidazolidine-2,4-dione (228 mg, 2.0 mmol) and K_2CO_3 (332 mg, 2.4 mmol) in DMF (15 mL) was added 1-(2-bromoethyl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (821 mg, 2.0 mmol). The resulting mixture was heated at 80°C for overnight. TLC was used to monitor the reaction. The reaction mixture was poured into 20 mL brine and extracted with EtOAc (40 mL X 3). The extracts were combined and washed with water, dried and concentrated in vacuo. The residue was firstly purified by column chromatography (DCM/MeOH = 100:1→30:1) to give the desired product as light yellow solid (780 mg, 88%). LC-MS[M+H]⁺-m/z 444.

Step 2: To the 25 mL hydrothermal synthesis reactor was added 3-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1-methylimidazolidine-2,4-dione (444 mg, 1.0 mmol), 37% formalin (3 mL), 2-Aminoethanol (1.0 mL) and THF (5 mL). The mixture was heated at 130°C for 24h. The reactor was cooled down to room temperature, and the inside solution was poured into water (10 mL), and extracted with EtOAc for twice. The combined extracts was washed with brine, dried over Na_2SO_4 , and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (DCM/CH₃OH = 200:1→10:1) to give the desired product as light yellow solid (35 mg, 8%). LC-MS[M+H]⁺-m/z 456.

Example 18

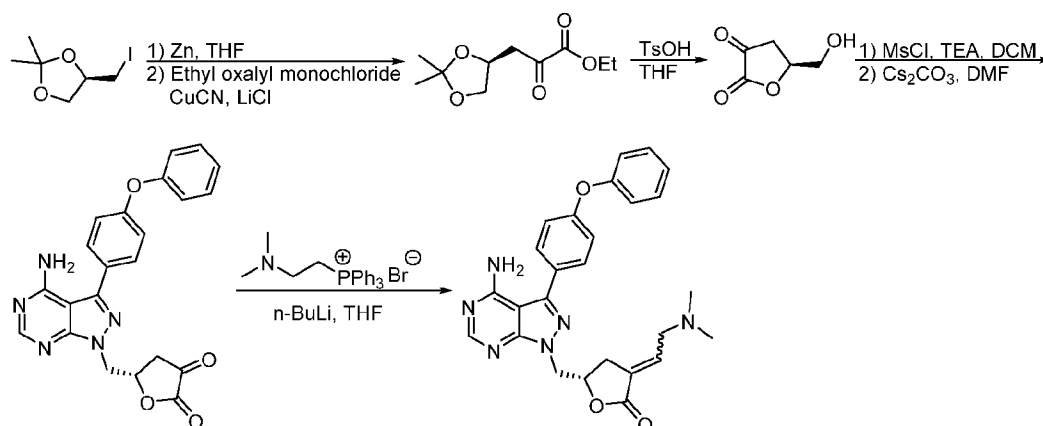
Synthesis of 3-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-5-methylenethiazolidine-2,4-dione



Similar procedure to the example 15 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 459.

Example 19

- 5 Synthesis of (S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-(dimethylamino)ethylidene)dihydrofuran-2(3H)-one



Step 1: To the dried 100 mL two-neck flask was added activated zinc powder (2.35 g, 36 mmol), and purged with nitrogen, followed by adding (R)-4-(iodomethyl)-2,2-dimethyl-1,3-dioxolane (4.36 g, 18 mmol) and THF (30 mL). The mixture was stirred at 45°C for overnight to afford a solution of organic zinc reagent.

To the other 250 mL dried three-neck flask was added CuCN (3.22 g, 36 mmol) and LiCl (3.05 g, 72 mmol), purged with nitrogen, and followed by adding THF (30 mL). The mixture was turned celadon during stirring. After 30 min, the mixture was cooled to -25°C, and added the above organic zinc reagent, and stirred at 0°C for 15 min, then recooled to -25 °C, and added Ethyl oxalyl monochloride (3.93 g, 28.8 mmol) dropwise. The resulting mixture was allowed to warm to room temperature and continued to stir for 3h. Then added saturated aqueous NH₄Cl (90 mL), and stirred

for 15 min. The mixture was extracted with EtOAc, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (PE/EA = 4:1) to afford a colorless oil (4.05 g, 65%).

Step 2: To the 100 mL flask was added ethyl (S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxopropanoate (2.16 g, 10.0 mmol), TsOH (516 mg, 3.0 mmol) and THF (50 mL). The resulting mixture was stirred for overnight, concentrated and purified by column chromatography to afford a colorless oil (1.11g, 85%).

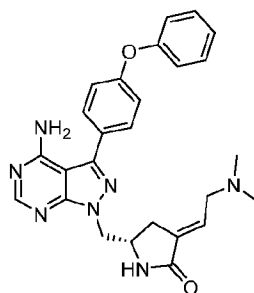
Step 3: To the solution of (S)-5-(hydroxymethyl)dihydrofuran-2,3-dione (1.11 g, 8.5 mmol) in DCM (30 mL) at 0°C was added and TEA (2.8 mL, 20.4 mmol), and stirred for 10 min, then carefully added MsCl (0.8 mL, 10.3 mmol) dropwise. The mixture was continued to stir for 3h, then washed with water and saturated NaHCO₃ (aq.) . The organic phase was dried and concentrated in vacuo to give the methanesulfonate.

To the suspension of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (909 mg, 3.0 mmol), Cs₂CO₃ (1.17 g, 3.6 mmol) in DMF (30 mL) was added the above methanesulfonate. The resulting mixture was stirred at room temperature for overnight. Poured into brine, and extracted with EtOAc. The combined organic phase was washed with water for twice, dried and concentrated in vacuo. The residue was purified by column chromatography to afford white solid (698 mg, 56%). LC-MS[M+H]⁺-m/z 416.

Step 4: To the suspension of 2-Dimethylaminoethyltriphenylphosphonium Bromide (622 mg, 1.5 mmol) in dry THF (30 mL) at -78°C was added n-BuLi (2.5 M in n-hexane, 0.6 mL) dropwise under the protection of nitrogen. The mixture was continued to stir for 30 min, then added the solution of (S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)dihydrofuran-2,3-dione (415 mg, 1.0 mmol) in THF (15 mL). The resulting mixture was allowed to warm to 0°C and stirred for overnight. Then added saturated NH₄Cl (aq., 20 mL), and extracted with EtOAc. The combined extracts were dried, concentrated and purified by column chromatography, then refined through PTLC and recrystallization from ether to give the desired product as white solid (71 mg, 15%).

Example 20

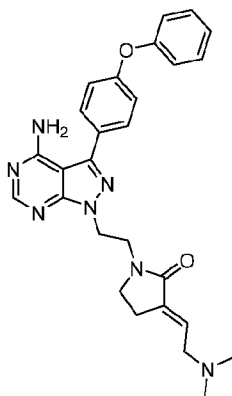
Synthesis of (*S,E*)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-(dimethylamino)ethylidene)pyrrolidin-2-one



- 5 Similar procedure to the example 19 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 470.

Example 21

Synthesis of (*E*)-1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-(2-(dimethylamino)ethylidene)pyrrolidin-2-one



10

Similar procedure to the example 2 was followed to arrive at the title compound, with the LC-MS[M+H]⁺-m/z 484.

Example 22: Btk in vitro Inhibitory Activity

15 The Btk IC₅₀ of compounds disclosed herein was determined in a kinase assay as described below.

Btk kinase activity was determined using a time-resolved fluorescence resonance energy

transfer (TR-FRET) methodology. Measurements were performed in a reaction volume of 50 μ L using 96-well assay plates. The compound and Kinase were pre-incubated for 30min and then substrate (SRCtide: HDB, Cat# FS-1C)/ATP(Sigma, Cat# A7699) mixture was added, and continued to incubate in a reaction buffer composed of 100 mM HEPES, 10 mM $MgCl_2$, 100 μ L/L Brij35 (30%), 1 mM DTT at pH 7.4 at 30 °C for 1 hour. The reaction in each well was quenched by the addition of 20 μ L of 35mM EDTA (relative to divalent cation) and 26 μ L stopped reaction in each well was transferred to a 384-well assay plate and read by EZ Reader II. Reading values were compared to 100% inhibition effect controls and 0% inhibition effect controls, and the inhibition percentages were calculated. The IC_{50} value for each compound was then calculated based on a 9 point concentration-dependent inhibition curve. The IC_{50} data for representative compounds were illuminated as follows (Table 1).

Table 1

Compound	Btk IC_{50} (nM)
Example 4	++
Example 5	+++
Example 6	+++
Example 9	++
Example 12	+++
Example 14	+
Example 15	+++
Example 17	+++
Example 20	+

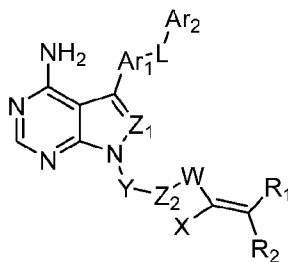
Footnote: +++: ≤ 50 nM; ++:51-500nM; +: ≥ 500 nM, but <10 uM.

Although the present invention has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible. Therefore, the spirit and scope of the present invention should not be limited to the description of the preferred versions described herein. All features disclosed in the specification, including the abstract and drawings, and all the steps in any method or process disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. Each feature disclosed in the

specification, including abstract and drawings, can be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features. Various modifications of the invention, in addition to those described herein, will be
5 apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference cited in the present application is herein incorporated by reference in its entirety.

THE CLAIMS

1. A compound of Formula (I), or pharmaceutically acceptable salts thereof:



Formula (I)

- 5 Wherein:

L is selected from CH₂, O, NR₃ or S(O)_x, wherein x is 0, 1 or 2;

Wherein R₃ is H, C₁-C₅ alkyl or substituted C₁-C₅ alkyl.

Ar₁, Ar₂ are independently selected from aryl, substituted aryl, heteroaryl or substituted heteroaryl;

- 10 Z₁ is selected from N or CR₄;

Wherein R₄ is selected from H, halogen, C₁-C₅ alkyl, substituted C₁-C₅ alkyl, C₁-C₈ heteroalkyl, substituted C₁-C₈ heteroalkyl, CN, C(O)(C₁-C₈ alkyl), and C(O)O(C₁-C₈ alkyl).

Y is selected from C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₁-C₈ heteroalkyl, substituted C₁-C₈ heteroalkyl, C₃-C₁₀ cycloalkyl, substituted C₃-C₁₀ cycloalkyl, C₂-C₁₀ heterocycloalkyl, substituted C₂-C₁₀ heterocycloalkyl, C₁-C₅alkyl(C₃-C₁₀)cycloalkyl and substituted C₁-C₅alkyl(C₃-C₁₀)cycloalkyl.

Z₂ is selected from N or CR₅;

Wherein R₅ is selected from H, halogen, C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₁-C₈ heteroalkyl, substituted C₁-C₈ heteroalkyl, and hydroxy.

- 20 W is selected from C₁-C₅ alkyl, substituted C₁-C₅ alkyl, C₁-C₅ heteroalkyl, substituted C₁-C₅ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O), C(O)N(R₆), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄ alkenyl;

Wherein R₆ is selected from H, C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl and substituted C₃-C₁₀ cycloalkyl; R₇ is selected from H, NH₂, NH(C₁-C₈ alkyl), and NH(C₃-C₇ cycloalkyl).

X is selected from C(O), OC(O), NR₈C(O), C(S), S(O)₂, OS(O)₂, NR₈S(O)₂;

Wherein R₈ is selected from H, C₁-C₅ alkyl or substituted C₁-C₅ alkyl.

R₁ and R₂ are independently selected from H, halogen, C₁-C₈ alkyl, substituted C₁-C₈ alkyl, C₁-C₈heteroalkyl, substituted C₁-C₈ heteroalkyl, C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, C₂-C₆ heterocycloalkyl, substituted C₂-C₆ heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C₁-C₄ alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₄ alkyl(C₃-C₇ cycloalkyl), C₁-C₄ alkyl(C₂-C₇ heterocycloalkyl).

2. The compound of Claim 1, wherein Z₁ is N.

3. The compound of Claim 1 or 2, wherein L is O.

10 4. The compound of Claim 1, 2 or 3, wherein R₁ and R₂ are independently selected from H, methyl and CH₂N(CH₃)₂.

5. The compound of Claim 4, wherein one of R₁ and R₂ is CH₂N(CH₃)₂, the other is H.

6. The compound of Claim 4, wherein R₁ and R₂ are each H.

15 7. The compound of Claim 1, 2 or 3, wherein Ar₁ and Ar₂ are independently selected from aryl and substituted aryl.

8. The compound of Claim 7, wherein Ar₁ is phenyl; Ar₂ is aryl or substituted aryl.

9. The compound of Claim 8, wherein R₁ and R₂ are independently selected from H, methyl and CH₂N(CH₃)₂.

10. The compound of Claim 8, wherein Ar₁ and Ar₂ are each phenyl.

20 11. The compound of Claim 10, wherein R₁ and R₂ are each H.

12. The compound of Claim 10, wherein one of R₁ and R₂ is CH₂N(CH₃)₂, the other is H.

13. The compound of Claim 12 or pharmaceutically acceptable salts thereof, wherein Y is C₁-C₃ alkyl, Z₂ is N or CH, X is C(O), OC(O) or NC(O), W is C₁-C₃ alkyl.

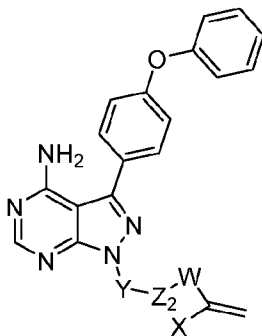
25 14. The compound of Claim 12 or pharmaceutically acceptable salts thereof, wherein Y is C₁-C₃ alkyl, Z₂ is N or CH, X is C(O) or NC(O), W is C₁-C₃ alkyl.

15. The compound of Claim 14 or pharmaceutically acceptable salts thereof, wherein Y is C₁-C₂ alkyl, Z₂ is CH, X is NC(O), W is C₁-C₂ alkyl.

16. The compound of Claim 14 or pharmaceutically acceptable salts thereof, wherein Y is C₁-C₃ alkyl, Z₂ is N, X is C(O), W is C₂-C₃ alkyl.

30 17. The compound of Claim 1 or pharmaceutically acceptable salt thereof, wherein the compound

is a compound of Formula (Ia),



Formula (Ia)

Wherein:

5 Y is selected from C₁-C₅ alkyl or substituted C₁-C₅ alkyl.

Z₂ is selected from N or CR₅;

Wherein R₅ is selected from H, halogen, C₁-C₃ alkyl, C₁-C₃ heteroalkyl, and hydroxy.

W is selected from C₁-C₅alkyl, substituted C₁-C₅alkyl, C₁-C₅ heteroalkyl, substituted C₁-C₅ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O), C(O)N(R₆), C(O)S, C(S)N(R₆),
 10 C(R₇)=N, and C₂-C₄alkenyl.

Wherein R₆ is selected from H, C₁-C₃alkyl, substituted C₁-C₃alkyl, C₃-C₆cycloalkyl and substituted C₃-C₆cycloalkyl; R₇ is selected from H, NH₂, NH(C₁-C₃ alkyl), and NH(C₃-C₆ cycloalkyl).

X is selected from C(O), OC(O), NR₈C(O), C(S), S(O)₂, OS(O)₂, NR₈S(O)₂;

15 Wherein R₈ is selected from H, C₁-C₃ alkyl, and substituted C₁-C₃ alkyl.

18. The compound of Claim 17, wherein X is selected from C(O), OC(O), NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl.

19. The compound of Claim 17 or 18, wherein W is selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), C(O)O, N(R₆)C(O), C(O)N(R₆), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄
 20 alkenyl. And R₆ is selected from H, methyl and ethyl; R₇ is selected from H, NH₂ and NHCH₃.

20. The compound of Claim 19, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.

21. The compound of Claim 17 or 18, wherein W is selected from C₁-C₄ alkyl, C₁-C₃ heteroalkyl, C(O)(C₀-C₃)alkyl, OC(O), N(R₆)C(O), C(O)S, C(S)N(R₆), C(R₇)=N, and C₂-C₄ alkenyl. And R₆ is
 25 selected from H, methyl and ethyl; R₇ is selected from H, NH₂ and NHCH₃.

22. The compound of Claim 21, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl.
23. The compound of Claim 17, wherein Y is selected from C₁-C₃ alkyl.
24. The compound of Claim 23, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.
- 5 25. The compound of Claim 23, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl.
26. The compound of Claim 23, wherein X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl.
27. The compound of Claim 26, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.
- 10 28. The compound of Claim 26, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl.
29. The compound of Claim 17 or 23, wherein Z₂ is selected from N and CH.
30. The compound of Claim 29, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.
31. The compound of Claim 29, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl.
- 15 32. The compound of Claim 29, wherein X is selected from C(O), OC(O), and NR₈C(O), and R₈ is selected from H, methyl, ethyl, propyl and isopropyl.
33. The compound of Claim 32, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.
34. The compound of Claim 33 or pharmaceutically acceptable salts thereof, wherein Y is selected
20 from C₁-C₂ alkyl; Z₂ is CH; X is selected from OC(O) and NR₈C(O), and R₈ is selected from H, methyl, ethyl; W is selected from C₁-C₃ alkyl.
35. The compound of Claim 33 or pharmaceutically acceptable salts thereof, wherein Y is selected from C₂-C₃ alkyl; Z₂ is N; X is C(O); W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl, C(O)O, C(O)N(CH₃) and C(O)S.
- 25 36. The compound of Claim 32, wherein W is selected from C₁-C₄ alkyl, C(O)(C₀-C₃)alkyl.
37. The compound of Claim 36 or pharmaceutically acceptable salts thereof, wherein Y is selected from C₁-C₂ alkyl; Z₂ is CH; X is selected from NR₈C(O), and R₈ is selected from H, methyl, ethyl; W is selected from C₁-C₂ alkyl.
38. The compound of Claim 36 or pharmaceutically acceptable salts thereof, wherein Y is selected
30 from C₂-C₃ alkyl; Z₂ is N; X is C(O); W is selected from C₂-C₄ alkyl.

39. The compound of Claim 36 or pharmaceutically acceptable salts thereof, wherein Y is selected from C₂-C₃ alkyl; Z₂ is N; X is C(O); W is selected from C(O)(C₀-C₃)alkyl.

40. The compound of Claim 36 or pharmaceutically acceptable salts thereof, wherein Y is selected from C₂-C₃ alkyl; Z₂ is selected from N and CH; X is NCH₃C(O) and OC(O); W is selected from
5 CH₂ and C(O).

41. A compound of Claim 1 or pharmaceutically acceptable salt thereof, wherein the compound is selected from:

(S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-methylenepyrrolidin-2-one

10 (R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-methylenepyrrolidin-2-one

(S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1-methyl-3-methylenepiperidin-2-one

15 (R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene dihydrofuran-2(3H)-one

(S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene dihydrofuran-2(3H)-one

5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenedihydrofuran-2(3H)-one

20 (R)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene pyrrolidin-2-one

5-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrrolidin-2-one

25 (S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylene piperidin-2-one

(S)-6-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methylenetetrahydro-2H-pyran-2-one

1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrrolidin-2-one

30 1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepiperidin-2-one

ridin-2-one

1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-methylenepi

peridin-2-one

1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepyrr

5 olidine-2,5-dione

1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methylenepipe

ridine-2,6-dione

3-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1-methyl-5-meth

yleneimidazolidine-2,4-dione

10 3-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-5-methylenethia

zolidine-2,4-dione

(S)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-(dimeth
ylamino)ethylidene)dihydrofuran-2(3H)-one

(S,E)-5-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-(dime

15 thylamino)ethylidene)pyrrolidin-2-one

(E)-1-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-(2-(dimeth

ylamino)ethylidene)pyrrolidin-2-one

42. Any compound according to any one of Claims 1-41, wherein the compound has a Btk
activation IC₅₀ value of 10 μM or less.

20 43. Any compound according to any one of Claims 1-41, wherein the compound has a Btk
activation IC₅₀ value of 1 μM or less.

44. A pharmaceutical composition, comprising a therapeutically effective amount of at least one
compound according to any one of Claims 1-41, and at least one pharmaceutically acceptable
excipient, adjuvant or carrier.

25 45. Use of the pharmaceutical composition of Claim 44 in manufacturing a medicament.

46. A method of modulating function of Btk receptor in animals or humans by administering to
the subject a therapeutically effective amount of at least one compound or pharmaceutically
acceptable salts thereof according to any one of Claims 1-41.

30 47. Use of at least any compound according to any one of Claims 1-41 or the pharmaceutical
composition of Claim 44 in manufacturing a medicament of modulating function of Btk receptor in

animals or humans.

48. Use of at least any compound according to any one of Claims 1-41 or the pharmaceutical composition of Claim 44 in manufacturing a medicament for the treatment of autoimmune diseases or conditions associated with aberrant B-cell proliferation such as rheumatoid arthritis, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions.

49. The use of Claim 48, wherein the autoimmune diseases associated with aberrant B-cell proliferation are selected from lymphoma, myeloma or leukemia.

50. Use of at least any compound according to any one of Claims 1-41 or the pharmaceutical composition of Claim 44 in the treatment of autoimmune diseases or conditions associated with aberrant B-cell proliferation such as rheumatoid arthritis, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions.

51. The use of Claim 50, wherein the autoimmune diseases associated with aberrant B-cell proliferation are selected from lymphoma, myeloma or leukemia.

52. A method of treatment of autoimmune diseases or conditions associated with aberrant B-cell proliferation such as rheumatoid arthritis, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions, comprising a therapeutically effective amount of at least one compound according to any one of Claims 1-41, or the pharmaceutical composition of Claim 44.

53. The method of Claim 52, wherein the autoimmune diseases associated with aberrant B-cell proliferation are selected from lymphoma, myeloma or leukemia.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2014/083765

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/519(2006.01)i; A61P 37/02(2006.01)i; A61P 19/02(2006.01)i; A61P 35/00(2006.01)i; A61P 35/02(2006.01)i; A61P 9/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K31, A61P37, A61P19, A61P35, A61P9

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNKI,CNABS,VEN,STN(RET,CAPLUS):pyrazolo, pyrimidine, Bruton, BTK

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012158795 A1 (PRINCIPIA BIOPHARMA INC) 22 November 2012 (2012-11-22) see abstract, claim 1, 19-20, example 3-5, description, page 4, lines 8-28, page 39, table1, page 109	1-53



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance
 “E” earlier application or patent but published on or after the international filing date
 “L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 “O” document referring to an oral disclosure, use, exhibition or other means
 “P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 “X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 “Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 “&” document member of the same patent family

Date of the actual completion of the international search

23 October 2014

Date of mailing of the international search report

19 November 2014

Name and mailing address of the ISA/CN

**STATE INTELLECTUAL PROPERTY OFFICE OF THE
P.R.CHINA(ISA/CN)
6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088 China**

Facsimile No. (86-10)62019451

Authorized officer

XING,Weiwei

Telephone No. (86-10)62086316

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2014/083765

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: **46,50-53**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
[1] Claims 46,50-53 are directed to methods of treatment of the human/animal body (Rule 39.1(iv) PCT).
Nonetheless, the search has been carried out based on the use of the compounds/composition in the manufacture of corresponding medicaments.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/CN2014/083765

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2012158795	A1	22 November 2012	US	2014221398	A1	07 August 2014