

(III)

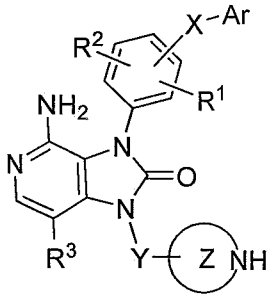
wherein:

R^1, R^2, R^3, X, Ar, Y, and Z are as defined in the first aspect above;

with a compound of formula $R^cCH=C(CN)COL$ where L is a leaving group under acylation reaction conditions where R^c is as defined in the first aspect above; or

(2). a compound of Formula (I) where R^a is hydrogen, A is $-CR^3-$ and other groups are as defined in the first aspect above: or a pharmaceutical salt thereof;

comprising reacting a compound of formula (III):



wherein:

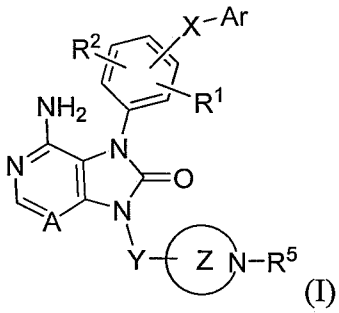
R^1, R^2, R^3, X, Ar, Y, and ring Z are as defined in the first aspect above;

with a compound of formula $R^cR^bC=CHCOL$ where L is a leaving group under acylation reaction conditions where R^b and R^c are as defined in the first aspect above;

(c) optionally making an acid addition salt of a compound obtained from Step (1) or (2) above;

(d) optionally making a free base of a compound obtained from Step (1) or (2) above.

In one aspect, there is provided a compound of Formula (I):



(I)

wherein:

R1 and R2 are independently hydrogen, alkyl, alkoxy, haloalkyl, or halo;

X is –O-;

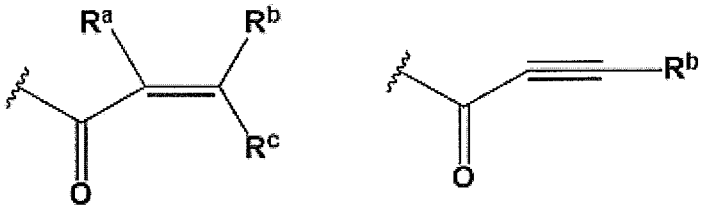
Ar is phenyl optionally substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, alkoxy, and hydroxy;

A is –CR3, - wherein R3 is hydrogen, alkyl, cyclopropyl, halo, haloalkyl, haloalkoxy, alkoxy, or cyano;

Y is bond or alkylene;

ring Z is heterocycloamino optionally substituted with one or two substituents independently selected from alkyl, hydroxy, alkoxy, and fluoro;

R5 is a group of formula (i) or (iv):



(i) (iv)

,

wherein:

R^a is hydrogen or fluoro;

each R^b independently is hydrogen or alkyl; and

R^c is hydrogen; and/or

a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound selected from the group consisting of:

(R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

(R)-4-amino-1-(1-(but-2-ynoyl)piperidin-3-yl)-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

(S)-1-((1-acryloylpyrrolidin-2-yl)methyl)-4-amino-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

(S)-4-amino-1-((1-(but-2-ynoyl)pyrrolidin-2-yl)methyl)-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one; and

(R)-4-amino-1-(1-(2-fluoroacryloyl)piperidin-3-yl)-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

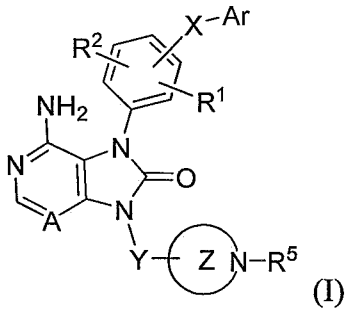
and/or a pharmaceutically acceptable salt of any of the foregoing compounds.

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this disclosure and have the following meaning:

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

R^1 and R^2 are independently hydrogen, alkyl, alkoxy, haloalkyl, or halo;

X is –O-;

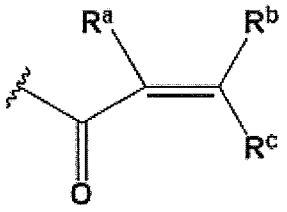
Ar is phenyl optionally substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, alkoxy, and hydroxy;

A is $–CR^3$, - wherein R^3 is hydrogen, alkyl, cyclopropyl, halo, haloalkyl, haloalkoxy, alkoxy, or cyano;

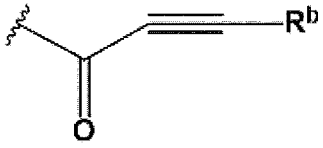
Y is bond or alkylene;

ring Z is heterocycloamino optionally substituted with one or two substituents independently selected from alkyl, hydroxy, alkoxy, and fluoro;

R^5 is a group of formula (i) or (iv):



(i)



(iv)

,

wherein:

R^a is hydrogen or fluoro;

each R^b independently is hydrogen or alkyl; and

R^c is hydrogen; and/or

a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

3. The compound of claim 1 or 2 and/or a pharmaceutically acceptable salt thereof, wherein -X-Ar is attached to carbon at the 4-position of the phenyl ring, the carbon of the phenyl ring attached to N of the cyclic urea ring being position 1.

4. The compound of any one of claims 1 to 3 and/or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently hydrogen or halo.

5. The compound of any one of claims 1 to 4 and/or a pharmaceutically acceptable salt thereof, wherein ring Z is piperidinyl wherein the carbon atom at the 3-position of the piperidinyl ring is attached to the nitrogen atom of the cyclic urea ring, and Y is a bond.

6. The compound of claim 5 and/or a pharmaceutically acceptable salt thereof, wherein the stereochemistry at carbon of the piperidinyl attached to the cyclic urea nitrogen is (R).

7. The compound of claim 5 and/or a pharmaceutically acceptable salt thereof, wherein the stereochemistry at the carbon of the piperidinyl attached to the cyclic urea nitrogen is (S).

8. The compound of any one of claim 1 or 6-7 and/or a pharmaceutically acceptable salt thereof, wherein R^5 is a group of formula (i).

9. A compound selected from the group consisting of:

(R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

(R)-4-amino-1-(1-(but-2-ynoyl)piperidin-3-yl)-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

(S)-1-((1-acryloylpyrrolidin-2-yl)methyl)-4-amino-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

(S)-4-amino-1-((1-(but-2-ynoyl)pyrrolidin-2-yl)methyl)-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one; and

(R)-4-amino-1-(1-(2-fluoroacryloyl)piperidin-3-yl)-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;

and/or a pharmaceutically acceptable salt of any of the foregoing compounds.

10. A pharmaceutical composition comprising a compound and/or a pharmaceutically acceptable salt of any one of claims 1 to 9 and a pharmaceutically acceptable excipient.

11. A pharmaceutical composition comprising a compound and/or a pharmaceutically acceptable salt of claim 9 and a pharmaceutically acceptable excipient.

12. Use of a compound and/or a pharmaceutically acceptable salt thereof of any one of claims 1 to 9 in the preparation of a medicament for inhibiting BTK in a mammal in need thereof.

13. Use of a compound and/or a pharmaceutically acceptable salt thereof of any one of claims 1 to 9 in the preparation of a medicament for treating an autoimmune disease, inflammatory disease, or cancer in a mammal in need thereof.

14. The use of claim 13 wherein the disease is acute necrotizing hemorrhagic leukoencephalitis, acute disseminated encephalomyelitis, autoimmune inner ear disease (AIED), autoimmune retinopathy, axonal & neuronal neuropathies, chronic inflammatory demyelinating polyneuropathy (CIDP), demyelinating neuropathies, Devic's disease (neuromyelitis optica), experimental allergic encephalomyelitis, giant cell arteritis (temporal arteritis), Guillain-Barre syndrome, Lambert-Eaton syndrome, chronic Meniere's disease, myasthenia gravis, neuromyotonia, opsoclonus-myoclonus syndrome, optic neuritis, paraneoplastic cerebellar degeneration, peripheral neuropathy, perivenous encephalomyelitis, restless legs syndrome, stiff person syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis/Giant cell arteritis, transverse myelitis, multiple sclerosis, dysautonomia, age-related macular degeneration (wet and dry), corneal transplantation, encephalitis, meningitis, vasculitis, or systemic lupus erythematosus (SLE).

15. The use of claim 13 wherein the disease is rheumatoid arthritis, psoriatic arthritis, lupus, uveitis, myasthenia gravis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, Sjogren's disease, Sjogren's dry eye, non-Sjogren's dry eye disease, psoriasis, pemphigus, urticaria, or asthma.

16. The use of claim 13 wherein the cancer is diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, small lymphocytic lymphoma (SLL), multiple myeloma, B-cell non-Hodgkin lymphoma, lymphoplamascytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis.