

Other diseases with an important role for dysfunctional B cells are B cell malignancies. Indeed anti-CD20 therapy is used effectively in the clinic for the treatment of follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia [Lim et al, *Haematologica*, **95** (2010) pp135-143]. The reported role for Btk in the regulation of proliferation and apoptosis of B cells indicates there is potential for Btk inhibitors in the treatment of B cell lymphomas as well. Inhibition of Btk seems to be relevant in particular for B cell lymphomas due to chronic active BCR signaling [Davis et al, *Nature*, **463** (2010) pp88-94].

Some classes of 6-5 membered fused pyridine ring compounds have been described as kinase inhibitors e.g. Imidazo[1,5-f][1,2,4]triazine compounds have been described in WO2005097800 and WO2007064993; Imidazo[1,5-a]pyrazine compounds have been described in WO2005037836 and WO2001019828 as IGF-1R enzyme inhibitors.

Some of the Btk inhibitors reported are not selective over Src-family kinases. With dramatic adverse effects reported for knockouts of Src-family kinases, especially for double and triple knockouts, this is seen as prohibitive for the development of Btk inhibitors that are not selective over the Src-family kinases. Both Lyn-deficient and Fyn-deficient mice exhibit autoimmunity mimicking the phenotype of human lupus nephritis. In addition, Fyn-deficient mice also show pronounced neurological defects. Lyn knockout mice also show an allergic-like phenotype, indicating Lyn as a broad negative regulator of the IgE-mediated allergic response by controlling mast cell responsiveness and allergy-associated traits [Odom et al, *J. Exp. Med.*, **199** (2004) pp1491-1502]. Furthermore, aged Lyn knock-out mice develop severe splenomegaly (myeloid expansion) and disseminated monocyte/macrophage tumors [Harder et al, *Immunity*, **15** (2001) pp603-615]. These observations are in line with hyperresponsive B cells, mast cells and myeloid cells, and increased Ig levels observed in Lyn-deficient mice.

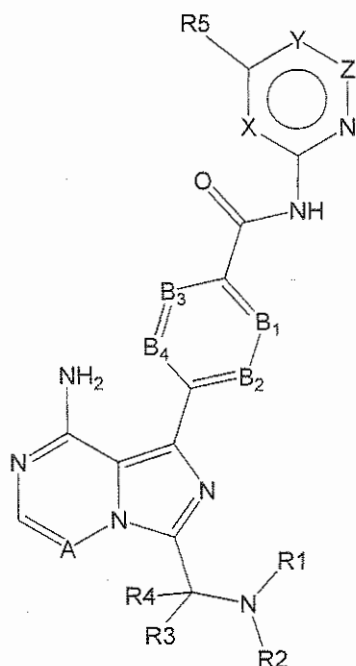
Female Src knockout mice are infertile due to reduced follicle development and ovulation [Roby et al, *Endocrine*, **26** (2005) pp169-176].

The double knockouts $\text{Src}^{-/-}\text{Fyn}^{-/-}$ and $\text{Src}^{-/-}\text{Yes}^{-/-}$ show a severe phenotype with effects on movement and breathing. The triple knockouts $\text{Src}^{-/-}\text{Fyn}^{-/-}\text{Yes}^{-/-}$ die at day 9.5 [Klinghoffer et al, *EMBO J.*, **18** (1999) pp2459-2471]. For the double knockout $\text{Src}^{-/-}\text{Hck}^{-/-}$, two thirds of the mice die at birth, with surviving mice developing osteopetrosis, extramedullary hematopoiesis, anemia, leukopenia [Lowell et al, *Blood*, **87** (1996) pp1780-1792].

Hence, an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.

Summary

In the first aspect, there is provided a compound according to Formula (I)



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is CH, N, O or S;

Y is C(R6), N, O or S;

Z is CH, N or a bond;

A is CH or N;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or C(R9);

B4 is N or C(R10);

R1 is R11C(O), R12S(O), R13SO₂ or (1-6C)alkyl optionally substituted with R14;

R2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R2 and R3 form, together with the N atom that R2 is attached to and the C atom that R3 is attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R4 is H or (1-3C)alkyl;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R6 is H or (1-3C)alkyl; or

R5 and R6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R7 is H or halogen;

R8 is H or (1-3C)alkyl; or

R7 and R8 form, together with the C atom that R7 is attached to and the C atom that R8 is attached to, a (6-10C)aryl or (1-9C)heteroaryl;

R9 is H or halogen;

R10 is H, halogen or (1-3C)alkoxy;

R11 is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

R11 is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R12 and R13 are independently selected from the group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R14 is independently selected from the group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-

4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y cannot be O or S;
- when Z is CH or N then Y is C(R6) or N and X is CH or N;
- 0 to 2 atoms of B1, B2, B3 and B4 are N.

10 In another aspect, there is provided the compound as defined herein for use in therapy.

In another aspect, there is provided the compound as defined herein for use in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

15 In another aspect, there is provided the use of a compound as defined herein for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

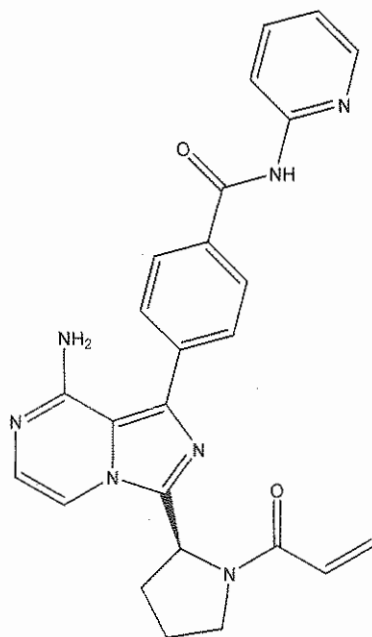
In another aspect, there is provided the use of the pharmaceutically acceptable salt as defined herein for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

In another aspect, there is provided a combination of a compound as defined herein and a further therapeutic agent.

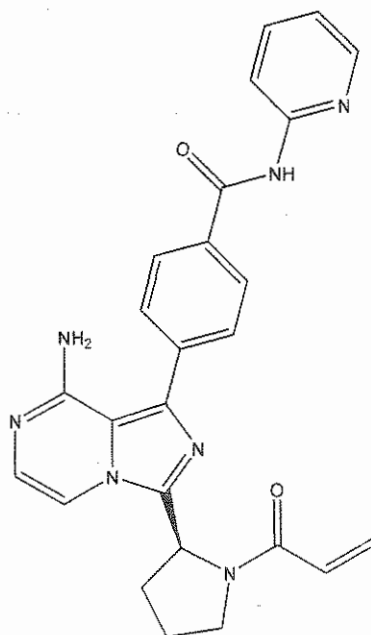
25 In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable excipient.

In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound as defined herein.

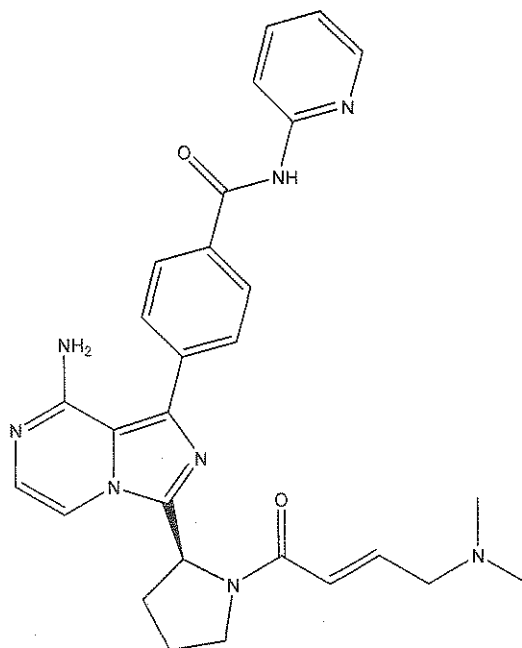
30 In another aspect, there is provided a compound which is (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



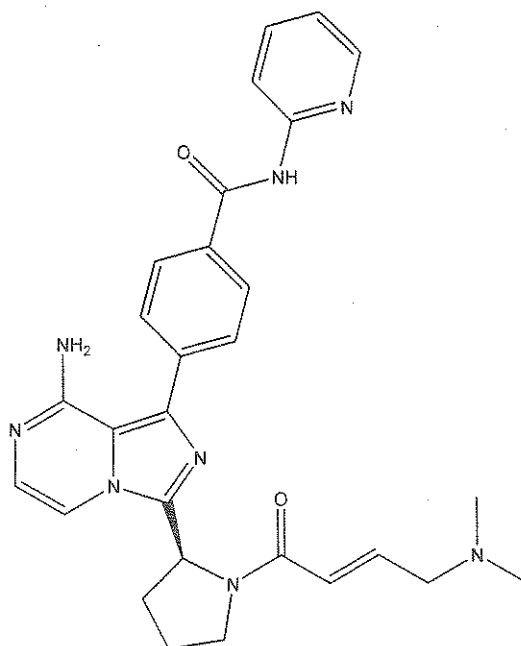
In another aspect, there is provided a pharmaceutically acceptable salt of a compound, the compound being (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:



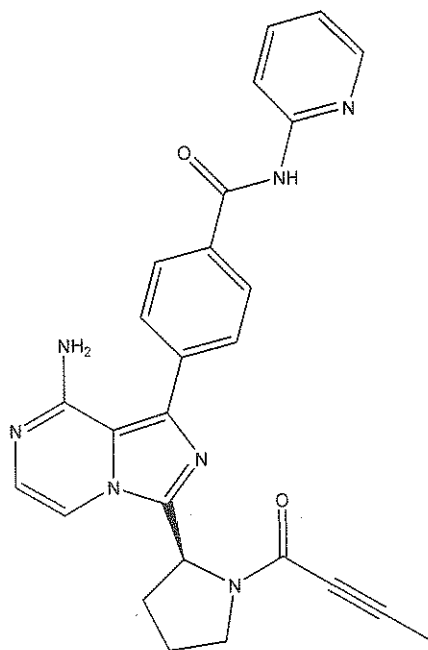
In another aspect, there is provided a compound which is (*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



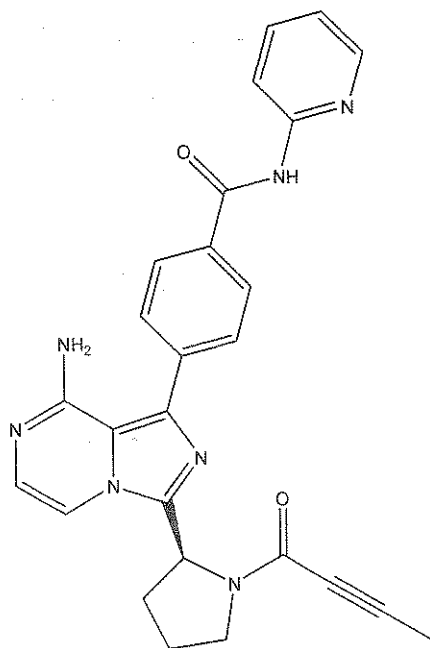
In another aspect, there is provided a pharmaceutically acceptable salt of a compound, the compound being (S,E)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:



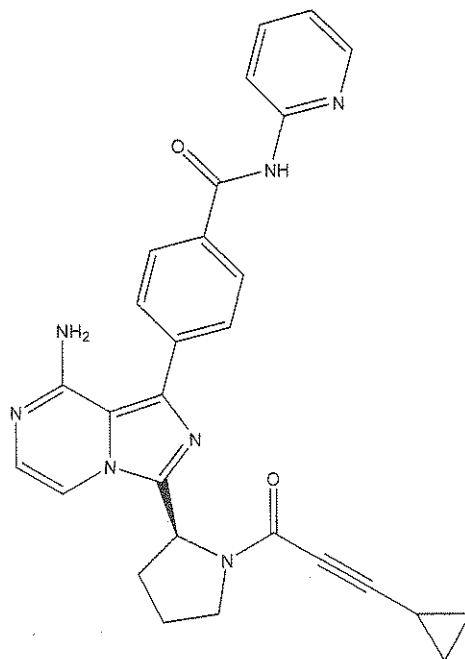
In another aspect, there is provided a compound which is (S)-4-(8-amino-3-(1-but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



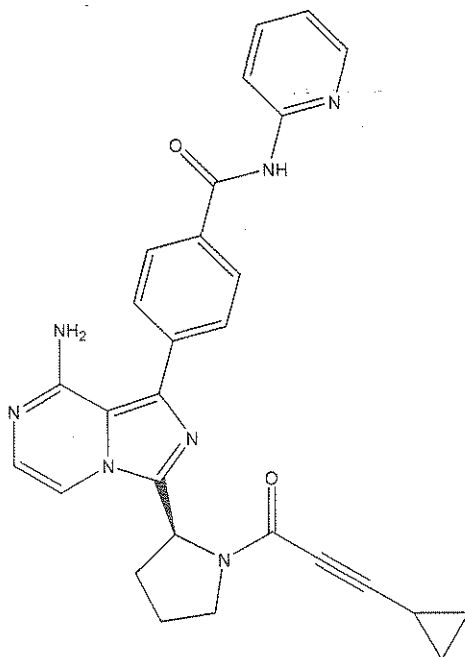
In another aspect, there is provided a pharmaceutically acceptable salt of a compound, the compound being (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:



In another aspect, there is provided a compound which is (*S*)-4-(8-amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:

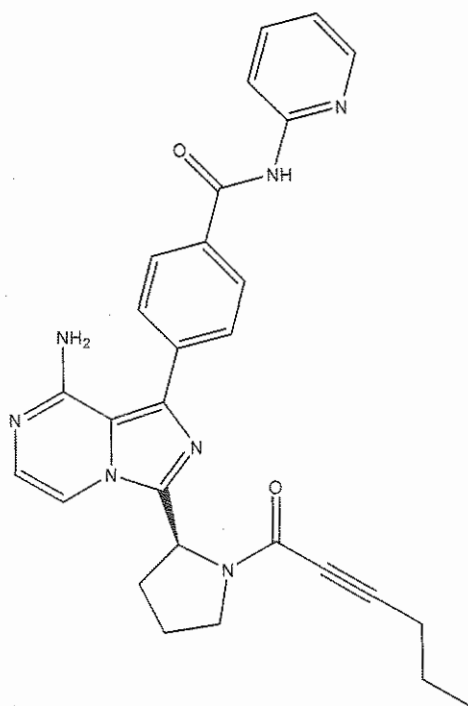


In another aspect, there is provided a pharmaceutically acceptable salt of a compound, the compound being (S)-4-(8-amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:



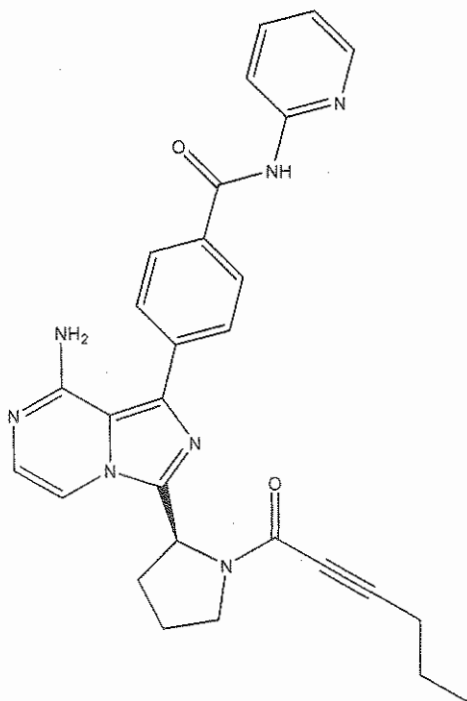
In another aspect, there is provided a compound which is (S)-4-(8-amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:

2h



In another aspect, there is provided a pharmaceutically acceptable salt of a compound, the compound being (*S*)-4-(8-amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-

5 N-(pyridin-2-yl)benzamide and having the structure:

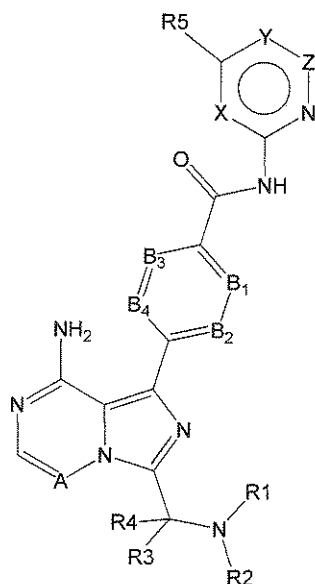


Detailed description of the invention

The object of the present invention is to provide 6-5 membered fused pyridine ring compounds, to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the

Claims

1. ~~A Compound~~ compound according to ~~formula~~ Formula (I)



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

X is CH, N, O or S;

Y is C(R6), N, O or S;

Z is CH, N or a bond;

A is CH or N;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or C(R9);

B4 is N or C(R10);

R1 is R11C(O), R12S(O), R13SO₂ or (1-6C)alkyl optionally substituted with R14;

R2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R2 and R3 form, together with the N atom that R2 is attached to and the C atom that R3 is they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R4 is H or (1-3C)alkyl;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R6 is H or (1-3C)alkyl; or

R5 and R6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R7 is H, or halogen ~~or (1-3C)alkoxy~~;

R8 is H or (1-3C)alkyl; or

R7 and R8 form, together with the ~~carbon C~~ atom that R7 is attached to and the C atom that R8 is ~~they are attached to,~~ a (6-10C)aryl or (1-9C)heteroaryl;

R9 is H, or halogen ~~or (1-3C)alkoxy~~;

R10 is H, halogen or (1-3C)alkoxy;

R11 is independently selected from ~~a~~ the group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

R11 is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R12 and R13 are independently selected from ~~a~~ the group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R14 is independently selected from ~~a~~ the group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can-not be O or S;

- when Z is CH or N then Y is C(R6) or N and X is CH or N;
- 0 to 2 atoms of B1, B2, B3 and B4 are N.

2. The compound according to claim 1 wherein B1 is C(R7); B2 is C(R8); B3 is C(R9); B4 is C(R10);

R7 is H, R9 is H, and R10 ~~each are~~ is H; and

R8 is selected from ~~a~~ the group consisting of hydrogen and methyl.

3. The compound according to any one of claims 1 to 2 wherein R4 is selected from ~~a~~ the group consisting of hydrogen and methyl.

4. The compound according to any one of claims 1 to 3 wherein the ring containing X, Y and Z is selected from ~~a~~ the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl, and isoxazolyl.

5. The compound according to any one of claims 1 to 4 wherein the ring containing X, Y and Z is selected from ~~a~~ the group consisting of pyridyl, pyrimidyl, and thiazolyl.

6. The compound according to any one of claims 1 to 5 wherein R5 is selected from ~~a~~ the group consisting of hydrogen, fluorine, chlorine, (1-3C)alkyl and (1-2C) alkoxy; the (1-3C)alkyl group of which is optionally substituted with one or more halogen.

7. The compound according to any one of claims 1 to 6 wherein R5 is selected from ~~a~~ the group consisting of hydrogen, fluorine, methyl, ethyl, propyl, methoxy and trifluoromethyl.

8. The compound according to any one of claims 1 to 7 wherein R2 is hydrogen or (1-3C)alkyl; and R3 is (1-6C)alkyl.

9. The compound according to any one of claims 1 to 7 wherein R2 and R3 ~~together form,~~ together with the N atom that R2 is attached to and the C atom that R3 is attached to, a

heterocycloalkyl ring selected from azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl, optionally substituted with one or more fluoro, hydroxyl, (1-3C) alkyl, (1-3C)alkoxy, or oxo.

- 5 | 10. The compound according to any one of claims 1 to 9 wherein R1 is R11C(O) and R11 is
independently selected from ~~a~~the group consisting of (1-6C)alkyl, (2-6C)alkenyl or (2-
6C)alkynyl each optionally substituted with one or more groups selected from hydroxyl,
10 | (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy,
(3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or R11 is (1-5C)heteroaryl
optionally substituted with one or more groups selected from halogen or cyano.
- 15 | 11. The compound according to any one of claims 1 to 10 wherein R1 is R11C(O) and R11 is
selected from ~~a~~the group consisting of (2-6C)alkenyl or (2-6C)alkynyl each optionally
substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-
7C)cycloalkyl, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy or (3-
7C)heterocycloalkyl.

12. ~~Compound~~ The compound according to claim 1 selected from a ~~the~~ group consisting of
- (*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
- (*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;
- (*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
- (*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
- (*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide;
- (*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;
- (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide;
- ~~(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide;~~
- (*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide;
- (*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

- (*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
- (*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;
- 5 (*S*)-4-(8-Amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
- (*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide ;
- (*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide ;
- 10 (*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide ;
- (*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide ;
- 15 (*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide ;
- (*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide;
- (*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide;
- 20 ~~(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide;~~
- 4-(8-Amino-3-((*S*)-1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;
- 25 4-(3-(Acrylamidomethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-4-(8-Amino-3-(1-but-2-ynamidoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-*S*-2-(2-(8-Amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidin-1-yl)-2-oxoethyl ethanethioate;
- 30 (*S*)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-4-(8-Amino-3-(1-(6-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

- (*S*)-4-(8-Amino-3-(1-pent-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-4-(8-Amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- 5 (*S*)-4-(8-Amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- 4-(3-(1-Acryloylazepan-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*R*)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-
- 10 (pyridin-2-yl)benzamide ;
- (*S*)-4-(8-amino-3-(1-(*N*-methylbut-2-ynamido)ethyl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
- (*S*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- 15 (*S*)-4-(8-Amino-3-(1-(4-methoxybut-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
- (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-N-(4-
- 20 (pyrrolidin-1-yl)pyridin-2-yl)benzamide;
- (*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
- (*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- 25 (*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
- (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
- (*S,E*)-4-(8-amino-3-(1-(4-methoxy-*N*-methylbut-2-enamido)ethyl)imidazo[1,5-*a*]pyrazin-
- 30 1-yl)-N-(4-propylpyridin-2-yl)benzamide;
- (*S*)-4-(8-amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
- (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-methoxypyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-fluoro-*N*-(4-methoxypyridin-2-yl)benzamide;

5 (*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-fluoropyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(isoxazol-3-yl)benzamide;

10 (*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyrimidin-2-yl)benzamide;

4-(8-amino-3-((*S*)-1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-3-methyl-*N*-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-methylpyridin-2-yl)benzamide;

15 (*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-isopropylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-methylpyridin-2-yl)benzamide;

20 (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(thiazol-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-propylpyridin-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

25 (*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-propylpyridin-2-yl)benzamide;

30 (*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-isopropylpyridin-2-yl)benzamide;

4-(8-amino-3-((*S*)-1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-3-methyl-*N*-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-fluoro-*N*-(4-propylpyridin-2-yl)benzamide;

4-(3-((*S*)-1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;

(*E*)-4-(8-amino-3-((4-(dimethyl amino)but-2-enamido)methyl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

5 (*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

10 (*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide;

15 (*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)-N-methylbut-2-enamido)ethyl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

20 (*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

25 (*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

30 ~~(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide;~~

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide;

4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide;

5 4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-3-methyl-N-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide;

10 (*S*)-4-(8-amino-3-(1-but-2-ynoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-methacryloylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

15 (*S*)-4-(8-amino-3-(1-(2-(trifluoromethyl)acryloyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-but-2-enoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

20 (*S*)-4-(8-amino-3-(1-(cyanomethyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*E*)-4-(8-amino-3-((4-methoxybut-2-enamido)methyl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide;

25 (*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)azepan-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;

30 ~~(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide;~~

(*S*)-4-(3-(1-acrylamidoethyl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-isopropylpyridin-2-yl)benzamide;

~~(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-methoxy-*N*-(pyridin-2-yl)benzamide;~~

(*S,E*)-4-(8-amino-3-(1-cinnamoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide;

(*S*)-*N*-(1-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-*a*]pyrazin-3-yl)ethyl)-2-chloropyrimidine-4-carboxamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-fluoropyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

~~(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-methoxy-*N*-(4-propylpyridin-2-yl)benzamide;~~

~~(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-methoxy-*N*-(4-propylpyridin-2-yl)benzamide;~~

4-(8-amino-3-(but-2-ynamidomethyl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(*N*-methylbut-2-ynamido)ethyl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-2-fluoro-*N*-(4-propylpyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(5-ethylthiazol-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-*a*]pyrazin-1-yl)-*N*-(5-ethylthiazol-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(5-ethylthiazol-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*R,E*)-4-(8-amino-3-(4-(4-methoxybut-2-enoyl)morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
5 (*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide;
10 (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
15 (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
20 (*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;
25 (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide ~~and~~
30 (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide, and
pharmaceutically acceptable salts of the foregoing.

13. The compound of any one of claims 1 to 12 for use in therapy.

14. The compound of any one of claims 1 to 12 for use in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

15. Use of a compound ~~of formula I~~ according to any one of the claims 1 to 12 ~~or a pharmaceutically acceptable salt thereof~~ for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

16. A combination of a compound of any one of claims 1 to 12, ~~or a pharmaceutically acceptable salt thereof~~, and a further therapeutic agent.

17. A pharmaceutical composition comprising a compound of any one of claims 1 to 12, ~~or a pharmaceutically acceptable salt thereof~~, and a pharmaceutically acceptable excipient.

18. The compound of ~~according to Formula I, or a pharmaceutically acceptable salt thereof,~~ according to claim 1, wherein
X is CH;
Y is CH;
~~and Z are~~ Z is CH;
 B1 is C(R7);
 B2 is C(R8);
 B3 is C(R9);
 B4 is C(R10);
 R1 is R11C(O);
 R2 and R3 form, together with the N atom that R2 is attached to and the C atom that R3 is attached to, a pyrrolidinyl;
 R4 is H;
R7 is H;
R9 is H;
~~and R10 is~~ R10 is H; and
 R8 is H or methyl.

19. The compound according to claim 1 selected from the group consisting of:
 (S)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
 (S,E)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

5 (*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S*)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

10 (*R*)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

15 (*S*)-4-(8-amino-3-(1-(*N*-methylbut-2-ynamido)ethyl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(S)-4-(8-amino-3-(1-but-2-ynoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide; ~~and~~

(S)-4-(8-amino-3-(1-but-2-ynoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide, and

pharmaceutically acceptable salts of the foregoing.

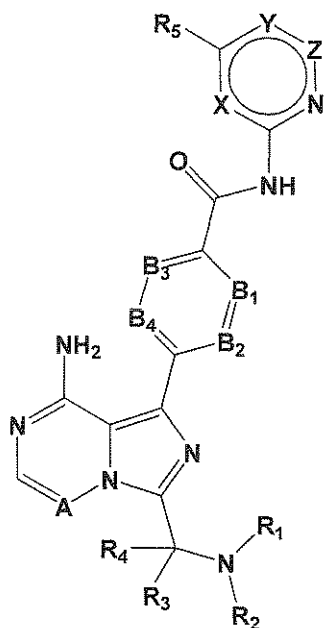
20. The use of claim 15, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, ~~and~~ spondylitis, glomerulonephritis ~~(with or without nephrotic syndrome)~~, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, ~~and~~ neutropenia, autoimmune gastritis, ~~and~~ autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, ~~(type I and type II diabetes)~~, acute active hepatitis, ~~(acute and chronic active hepatitis)~~, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, ~~(e.g. Behcet's disease)~~ chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, proliferative diseases, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signalling, ~~a proliferative mast cell disease~~, and a bone disorder related to multiple myeloma.

21. The use of claim 15, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, ~~or~~ and osteoarthritis.

22. The use of claim 15, wherein the Btk mediated disorder is selected from the group consisting of proliferative diseases, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, a ~~proliferative mast cell disease~~, and a bone disorder related to multiple myeloma.

5

23. A compound of Formula (I) according to claim 1:



Formula (I)

or a pharmaceutically acceptable salt thereof.

wherein:

X is CH or S;

Y is C(R6);

Z is CH or a bond;

A is CH;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or CH;

B4 is N or CH;

R1 is R11C(=O);

R2 is (1-3C)alkyl;

R3 is (1-3C)alkyl;

R2 and R3 form a (3-7C)heterocycloalkyl ring selected from the group consisting of azetidiny, pyrrolidinyl, piperidinyl, and morpholinyl, optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, or (1-3C)alkoxy;

R4 is H;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, or (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen;

R6 is H or (1-3C)alkyl;

R7 is H or halogen;

R8 is H or (C1-3)alkyl; or

R7 and R8 form, together with the carbon atom that R7 is attached to and the carbon atom that

R8 is attached to, a (6-10C)aryl or (1-9C)heteroaryl;

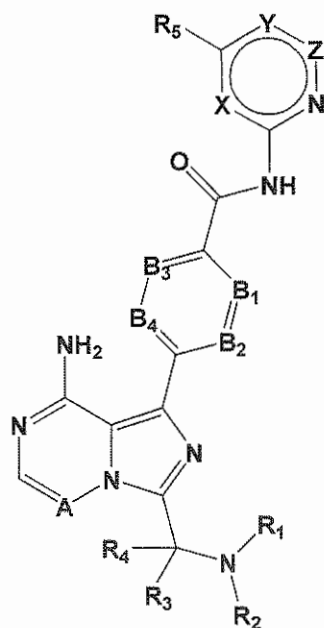
R5 and R6 together may form a (3-7C)cycloalkenyl or (2-6C)heterocycloalkenyl, each optionally substituted with (1-3C)alkyl or one or more halogen;

R11 is independently selected from the group consisting of (2-6C)alkenyl and (2-6C)alkynyl, wherein each alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl;

with the proviso that

0 to 2 atoms of B1, B2, B3 and B4 are N.

24. A compound of Formula (I) according to claim 1:



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl ;

A is CH ;

B1 is CH ;

B2 is CH ;

B3 is CH ;

B4 is CH ;

R1 is C(O)R11 ;

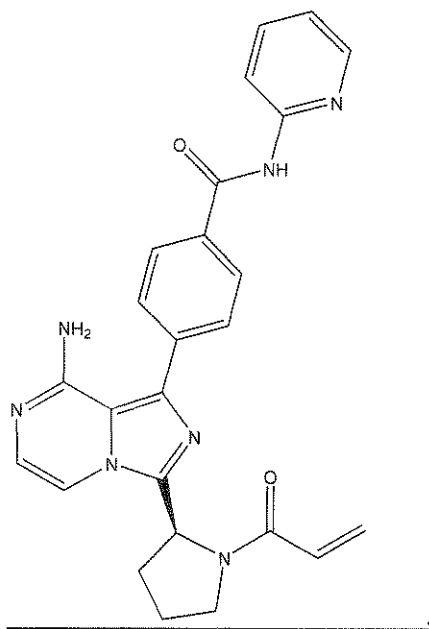
R2 and R3 form, together with the N atom that R2 is attached to and the C atom that R3 is attached to, a (3-7C)heterocycloalkyl ring selected from azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl, each optionally substituted with fluoro, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo ;

R4 is hydrogen ;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, or (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen ;

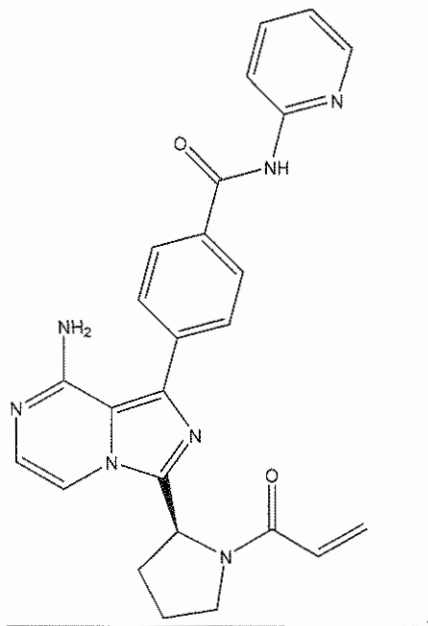
R11 is (2-6C)alkenyl or (2-6C)alkynyl, each optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, or (3-7C)heterocycloalkyl .

25. A compound which is (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide , having the structure:



26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of claim 25.

27. A pharmaceutically acceptable salt of a compound, the compound being (S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:

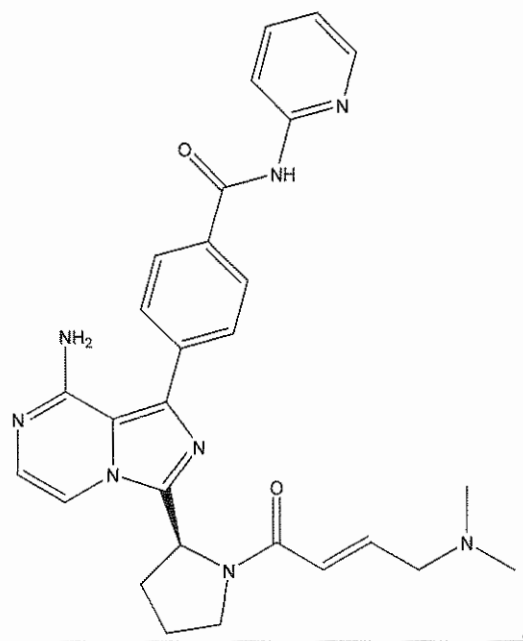


28. The pharmaceutically acceptable salt of claim 27, wherein the salt is selected from the group consisting of acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, fumarate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, phosphate, propionate, salicylate, succinate, sulfate, tartarate, thiocyanate, and toluenesulfonate.

29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 27.

30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 28.

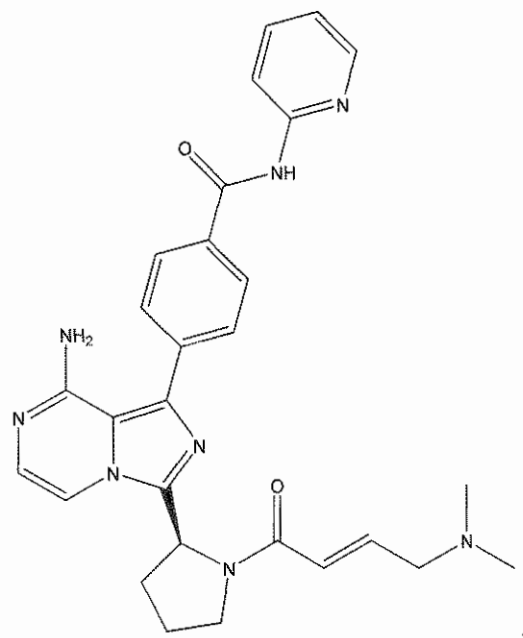
31. A compound which is (S,E)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of claim 31.

5

33. A pharmaceutically acceptable salt of a compound, the compound being (S,E)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:



10

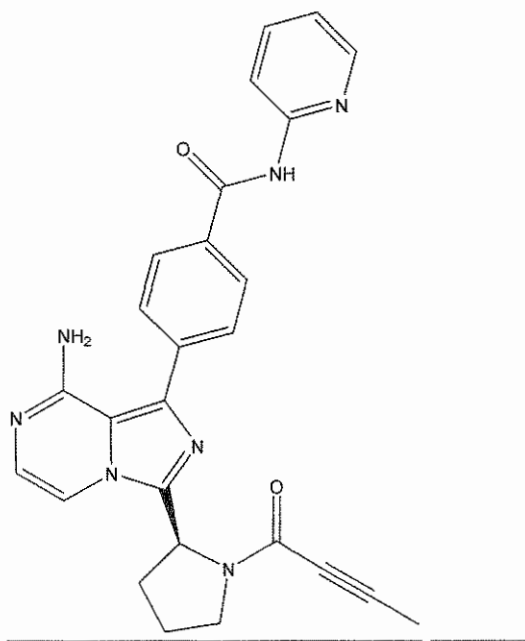
34. The pharmaceutically acceptable salt of claim 33, wherein the salt is selected from the group consisting of acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, borate,

butyrate, citrate, camphorate, camphorsulfonate, fumarate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, phosphate, propionate, salicylate, succinate, sulfate, tartarate, thiocyanate, and toluenesulfonate.

35. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 33.

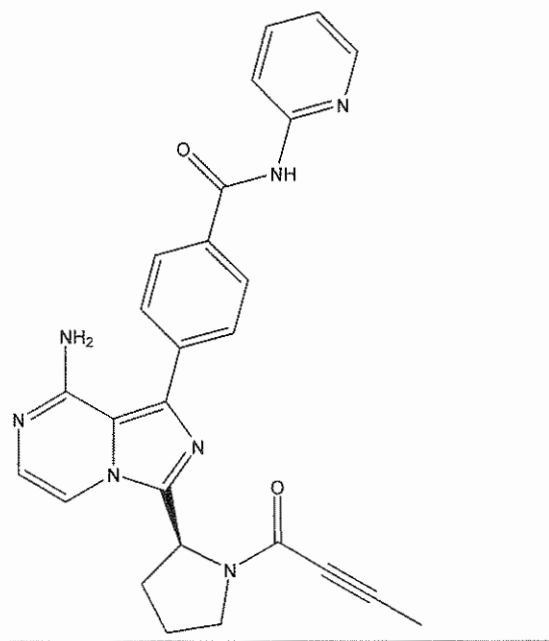
36. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 34.

37. A compound which is (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:

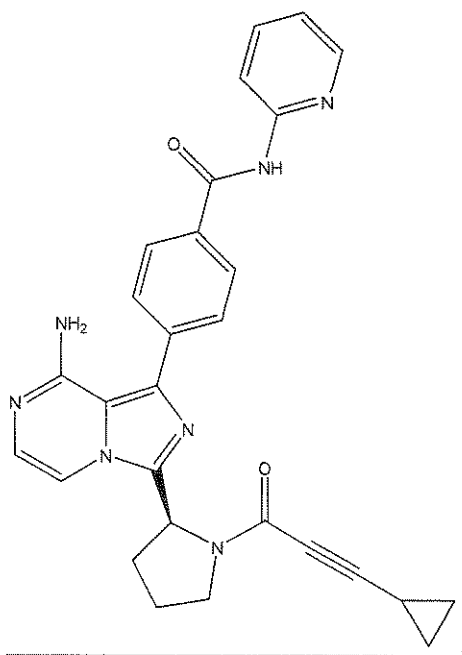


38. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of claim 37.

39. A pharmaceutically acceptable salt of a compound, the compound being (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:



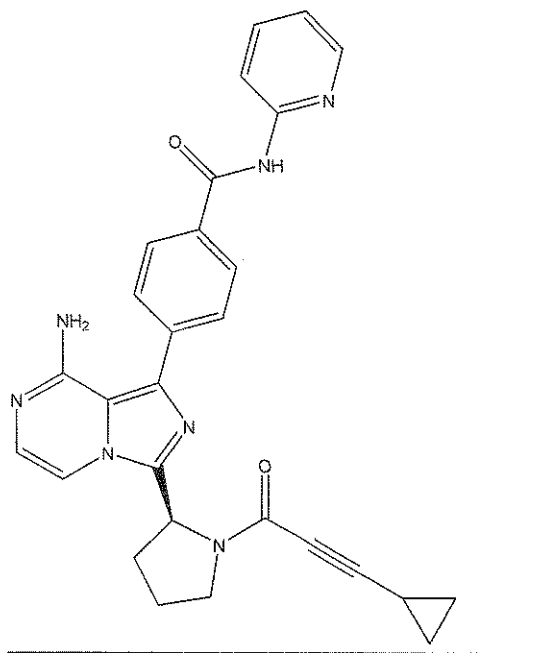
40. The pharmaceutically acceptable salt of claim 39, wherein the salt is selected from the group consisting of acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, fumarate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, phosphate, propionate, salicylate, succinate, sulfate, tartarate, thiocyanate, and toluenesulfonate.
41. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 39.
42. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 40.
43. A compound which is (S)-4-(8-amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



44. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of claim 43.

5

45. A pharmaceutically acceptable salt of a compound, the compound being (S)-4-(8-amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and having the structure:



10

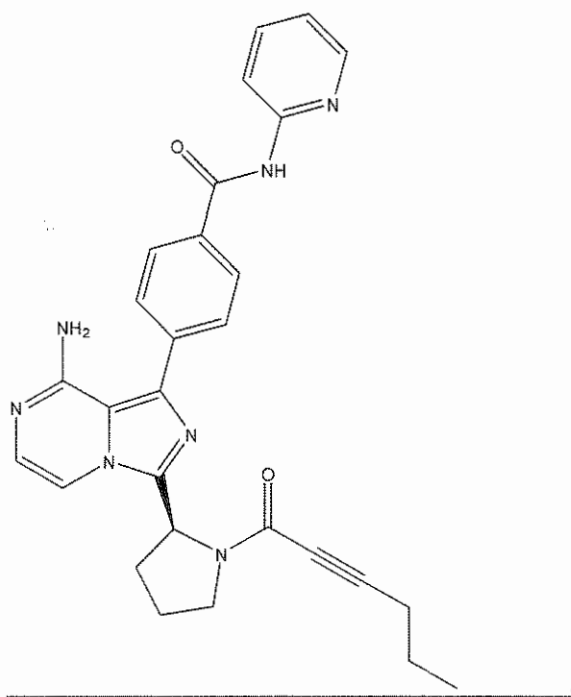
46. The pharmaceutically acceptable salt of claim 45, wherein the salt is selected from the group consisting of acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, borate,

butyrate, citrate, camphorate, camphorsulfonate, fumarate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, phosphate, propionate, salicylate, succinate, sulfate, tartarate, thiocyanate, and toluenesulfonate.

47. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 45.

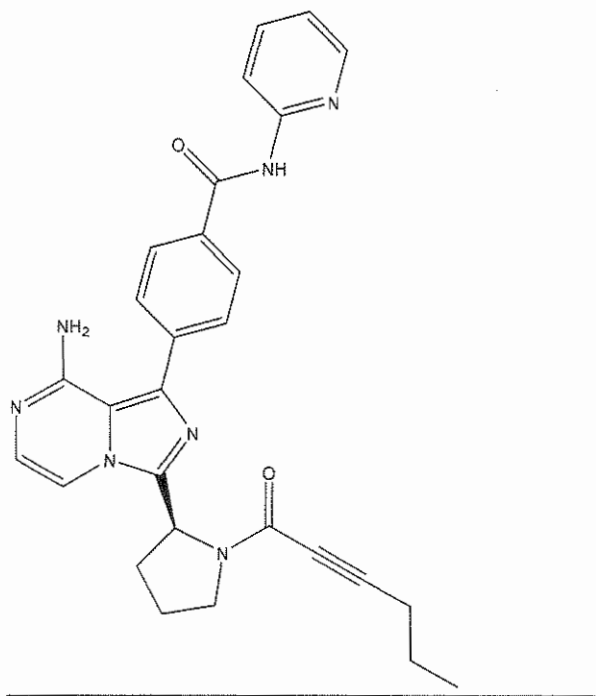
48. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 46.

49. A compound which is (*S*)-4-(8-amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide, having the structure:



50. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of claim 49.

51. A pharmaceutically acceptable salt of a compound, the compound being (*S*)-4-(8-amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide and having the structure:



52. The pharmaceutically acceptable salt of claim 51, wherein the salt is selected from the group consisting of acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, fumarate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, phosphate, propionate, salicylate, succinate, sulfate, tartarate, thiocyanate, and toluenesulfonate.
53. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 51.
54. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt of claim 52.
55. Use of the compound of claim 25 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.
56. The use of claim 55, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with

nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

57. The use of claim 55, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

58. Use of the pharmaceutically acceptable salt of claim 27 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

59. The use of claim 58, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis,

chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

60. The use of claim 58, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

61. Use of compound of claim 31 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

62. The use of claim 61, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis

media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

63. The use of claim 61, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

64. Use of the pharmaceutically acceptable salt of claim 33 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

65. The use of claim 64, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic

lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

66. The use of claim 64, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

67. Use of compound of claim 37 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

68. The use of claim 67, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

69. The use of claim 67, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

70. Use of the pharmaceutically acceptable salt of claim 39, for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

71. The use of claim 70, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

72. The use of claim 70, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

73. Use of compound of claim 43 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

74. The use of claim 73, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

75. The use of claim 73, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

76. Use of the the pharmaceutically acceptable salt of claim 45 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

77. The use of claim 76, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune

hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

78. The use of claim 76, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

79. Use of the compound of claim 49 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

80. The use of claim 79, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis,

multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

81. The use of claim 79, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.

82. Use of the pharmaceutically acceptable salt of claim 51 for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

83. The use of claim 82, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis,

sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma resulting from chronic active B cell receptor signaling, and a bone disorder related to multiple myeloma.

84. The use of claim 82, wherein the Btk mediated disorder is B cell chronic lymphocytic leukemia or mantle cell lymphoma.