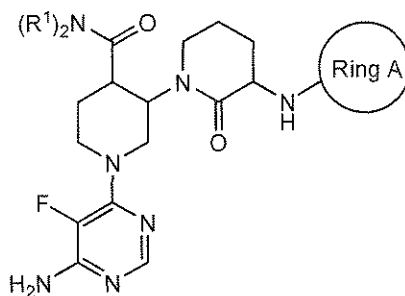


SUMMARY OF THE INVENTION

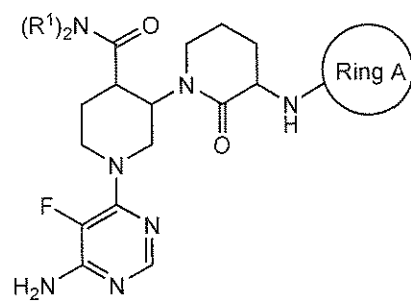
[0004] In certain embodiments, the present invention provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein R^1 and Ring A are as defined and described herein. Such compounds are inhibitors of the Tec kinase family, including Btk. Accordingly, provided compounds can be used in a variety of methods including *in vitro* screening and activity assays as well as *in vivo* pre-clinical, clinical, and therapeutic settings, as described in detail herein.

[0004a] In one aspect of the present disclosure, there is provided a compound of formula I:



I

or a pharmaceutically acceptable salt thereof,

wherein:

each R^1 is independently hydrogen, an optionally substituted C_{1-6} aliphatic group, an optionally substituted 3-7 membered monocyclic heterocyclic group, or an optionally

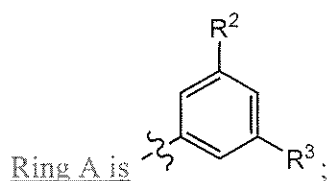
substituted heterocyclylalkyl group having 3-7 carbon atoms and 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or two R¹ groups are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein optionally substituted groups may be substituted with halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -C(O)R, -CO₂R, -N(R)C(O)OR, -C(O)N(R)₂, -OC(O)R, -N(R)C(O)R, -S(O)R, -S(O)₂R, or -S(O)₂N(R)₂;

each R is independently hydrogen or C₁₋₆ aliphatic;

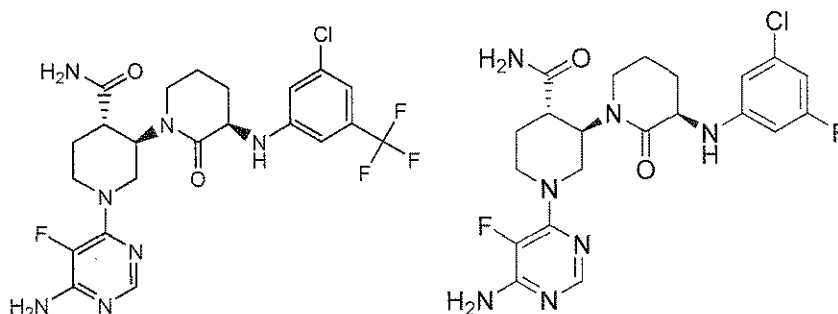
or two R groups attached to the same nitrogen are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms, in which any second heteroatom is independently selected from nitrogen, oxygen, or sulfur;



R² is -Cl or -F; and

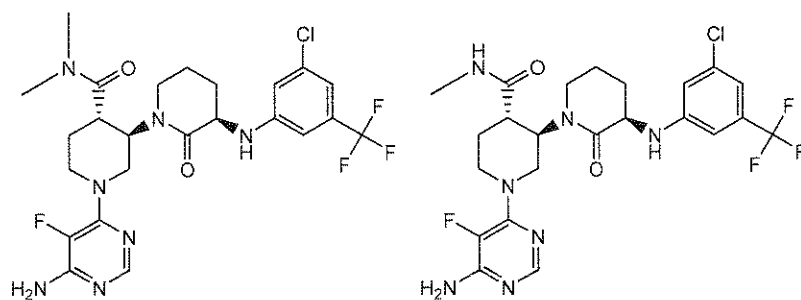
R³ is -CF₃, -OCF₃, or -F.

[0004b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:



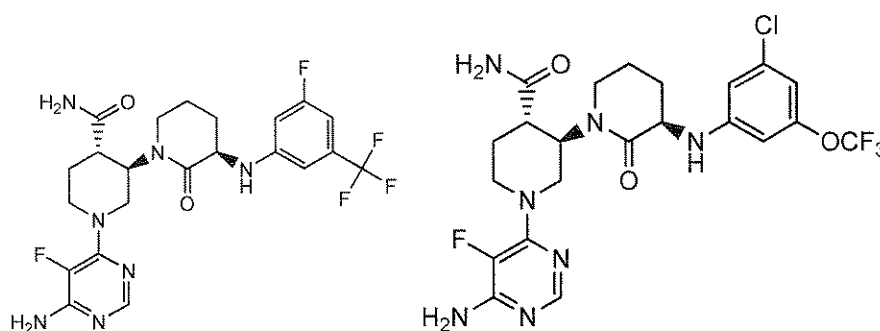
I-1

I-2



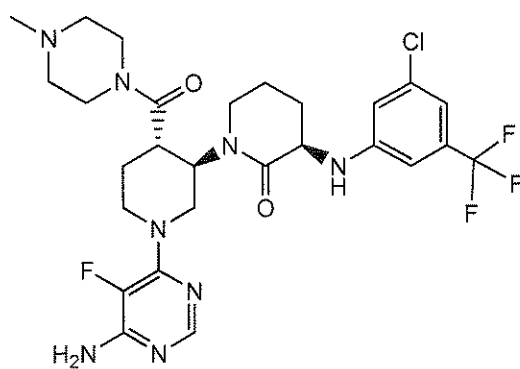
I-3

I-4



I-5

I-6



I-7

[0004c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or composition thereof, in the manufacture of a medicament for decreasing the enzymatic activity of Bruton's tyrosine kinase.

[0004d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or a composition thereof, in the manufacture of a medicament for treating a disorder responsive to inhibition of Bruton's tyrosine kinase.

[0004e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or a composition thereof, in the manufacture of a medicament for treating a disorder selected from the group consisting of autoimmune disorders, inflammatory disorders, and cancers.

[0004f] In another aspect of the present disclosure, there is provided an *ex vivo* method of decreasing the enzymatic activity of Bruton's tyrosine kinase comprising contacting Bruton's tyrosine kinase with an effective amount of a compound disclosed herein or a composition thereof.

[0005] In certain embodiments, the present ~~disclosure invention~~ provides pharmaceutical formulations comprising provided compounds.

[0006] In certain embodiments, the present ~~disclosure invention~~ provides a method of decreasing enzymatic activity of Btk. In some embodiments, such methods include contacting Btk with an effective amount of a Btk inhibitor.

[0007] In certain embodiments, the present ~~disclosure invention~~ provides a method of treating a disorder responsive to Btk inhibition in a subject in need thereof. Such disorders and methods are described in detail herein.

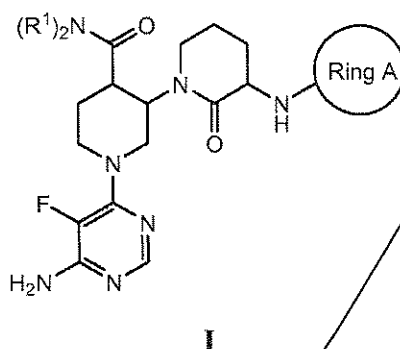
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0008] In certain embodiments, the present invention provides a compound of formula I:

Claims

What is claimed is:

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof,

wherein:

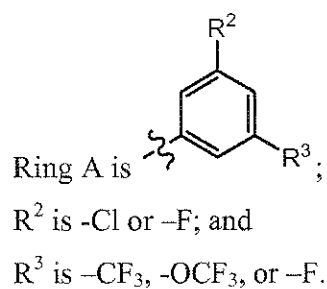
each R^1 is independently hydrogen, an optionally substituted C_{1-6} aliphatic group, an optionally substituted 3-7 membered monocyclic heterocyclic group, or an optionally substituted heterocyclalkyl group having 3-7 carbon atoms and 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

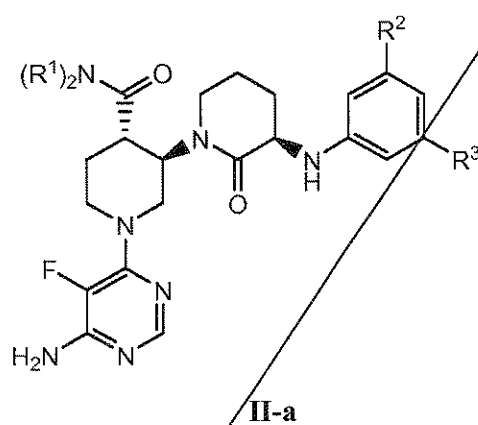
wherein optionally substituted groups may be substituted with halogen, $-NO_2$, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-C(O)R$, $-CO_2R$, $-N(R)C(O)OR$, $-C(O)N(R)_2$, $-OC(O)R$, $-N(R)C(O)R$, $-S(O)R$, $-S(O)_2R$, or $-S(O)_2N(R)_2$;

each R is independently hydrogen or C_{1-6} aliphatic;

or two R groups attached to the same nitrogen are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms, in which any second heteroatom is independently selected from nitrogen, oxygen, or sulfur;

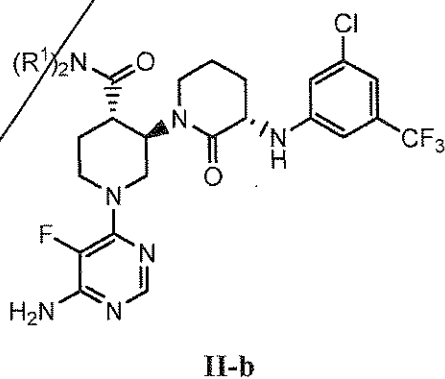


2. The compound of claim 1, wherein the compound is of formula **II-a**:



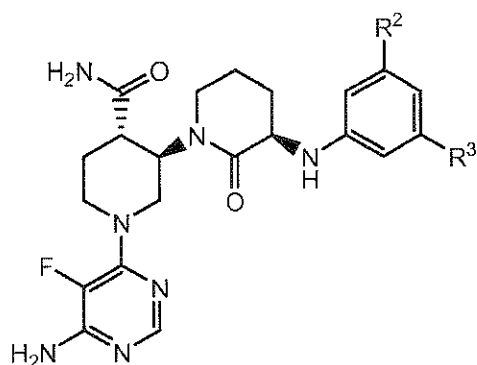
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is of formula **II-b**:



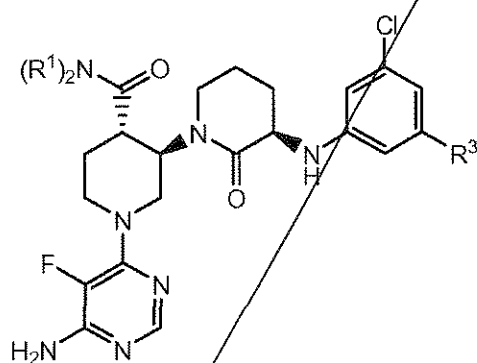
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is of formula **III**:



III

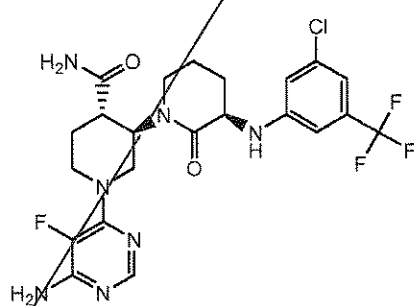
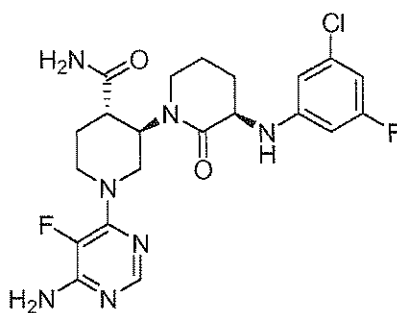
5. The compound of claim 1, wherein the compound is formula IV:

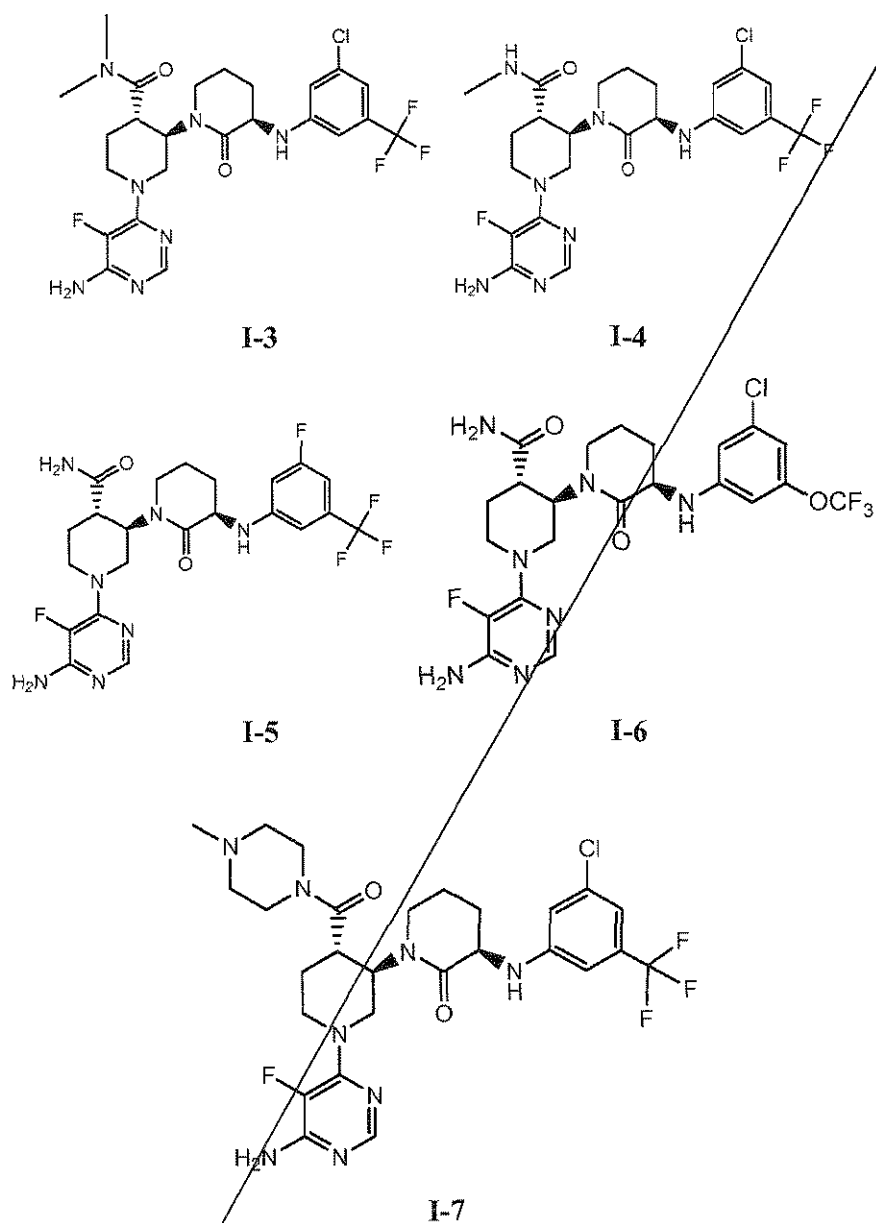


IV

6. The compound of claim 5, wherein R^3 is $-\text{CF}_3$.
7. The compound of claim 5, wherein R^3 is $-\text{F}$.
8. The compound of claim 5, wherein both R^1 are hydrogen.
9. The compound of claim 5, wherein one R^1 is hydrogen and the other R^1 is an optionally substituted C_{1-6} aliphatic.
10. The compound of claim 9, wherein one R^1 is hydrogen and the other R^1 is methyl.
11. The compound of claim 5, wherein both R^1 are optionally substituted C_{1-6} aliphatic groups.

12. The compound of claim 1, wherein one R^1 is hydrogen and the other an is optionally substituted C_{1-6} aliphatic.
13. The compound of claim 1, wherein both R^1 are optionally substituted C_{1-6} aliphatic groups.
14. The compound of claim 1, wherein both R^1 are hydrogen.
15. The compound of claim 1, wherein R^2 is $-Cl$.
16. The compound of claim 1, wherein R^2 is $-F$.
17. The compound of claim 1, wherein R^3 is $-CF_3$.
18. The compound of claim 1, wherein R^3 is $-OCF_3$.
19. The compound of claim 1, wherein R^3 is $-F$.
20. A compound selected from the group consisting of:

**I-1****I-2**



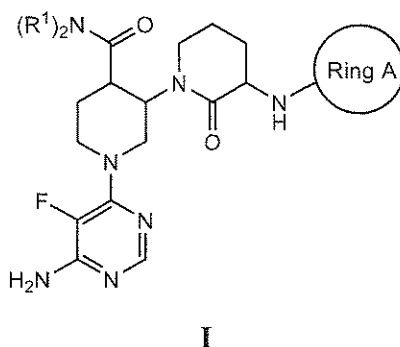
21. A method of decreasing the enzymatic activity of Bruton's tyrosine kinase comprising contacting Bruton's tyrosine kinase with an effective amount of a compound of any one of claims 1-20 or a composition thereof.

22. A method of treating a disorder responsive to inhibition of Bruton's tyrosine kinase comprising administering to a subject an effective amount of a compound of any one of claims 1-20 or a composition thereof.
23. A method of treating a disorder selected from the group consisting of autoimmune disorders, inflammatory disorders, and cancers comprising administering to a subject an effective amount of a compound of any one of claims 1-20 of a composition thereof.
24. The method of claim 23, wherein the disorder is rheumatoid arthritis.
25. The method of claim 23, wherein the disorder is systemic lupus erythematosus.
26. The method of claim 23, wherein the disorder is atopic dermatitis.
27. The method of claim 23, wherein the disorder is leukemia or lymphoma.

Claims

What is claimed is:

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof,

wherein:

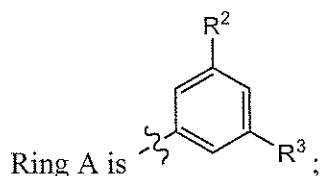
each R^1 is independently hydrogen, an optionally substituted C_{1-6} aliphatic group, an optionally substituted 3-7 membered monocyclic heterocyclic group, or an optionally substituted heterocyclalkyl group having 3-7 carbon atoms and 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein optionally substituted groups may be substituted with halogen, $-NO_2$, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-C(O)R$, $-CO_2R$, $-N(R)C(O)OR$, $-C(O)N(R)_2$, $-OC(O)R$, $-N(R)C(O)R$, $-S(O)R$, $-S(O)_2R$, or $-S(O)_2N(R)_2$;

each R is independently hydrogen or C_{1-6} aliphatic;

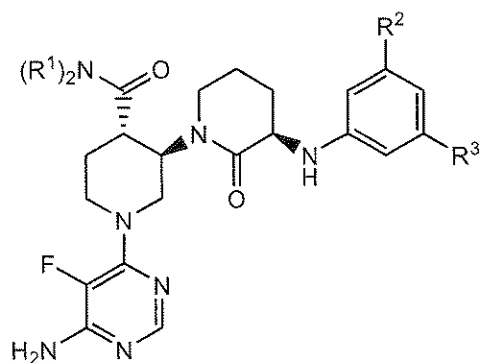
or two R groups attached to the same nitrogen are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms, in which any second heteroatom is independently selected from nitrogen, oxygen, or sulfur;



R^2 is $-Cl$ or $-F$; and

R^3 is $-\text{CF}_3$, $-\text{OCF}_3$, or $-\text{F}$.

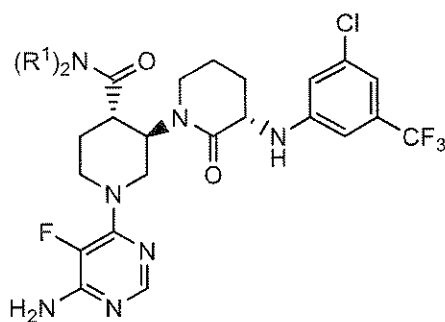
2. The compound of claim 1, wherein the compound is of formula **II-a**:



II-a

or a pharmaceutically acceptable salt thereof.

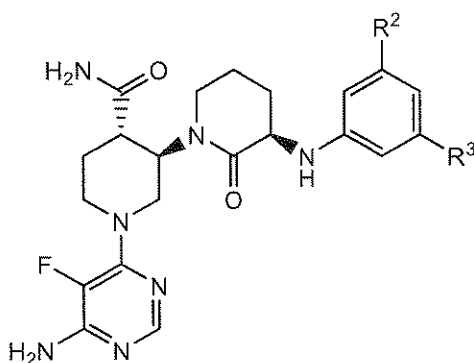
3. The compound of claim 1, wherein the compound is of formula **II-b**:



II-b

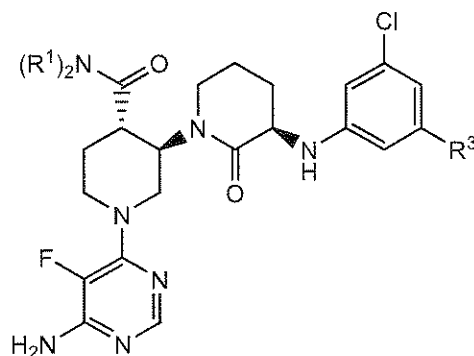
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is of formula **III**:



III

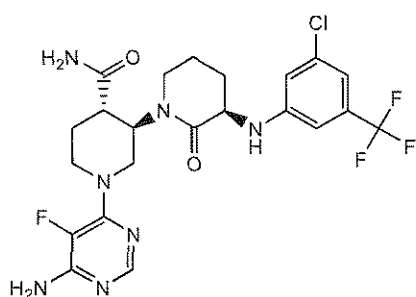
5. The compound of claim 1, wherein the compound is formula **IV**:



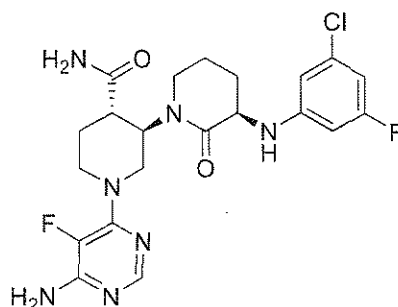
IV

6. The compound of claim 5, wherein R^3 is $-CF_3$.
7. The compound of claim 5, wherein R^3 is $-F$.
8. The compound of any one of claims 5 to 7, wherein both R^1 are hydrogen.
9. The compound of any one of claims 5 to 7, wherein one R^1 is hydrogen and the other R^1 is an optionally substituted C_{1-6} aliphatic.
10. The compound of claim 9, wherein one R^1 is hydrogen and the other R^1 is methyl.
11. The compound of any one of claims 5 to 7, wherein both R^1 are optionally substituted C_{1-6} aliphatic groups.
12. The compound of claim 1, wherein one R^1 is hydrogen and the other R^1 is optionally substituted C_{1-6} aliphatic.
13. The compound of claim 1, wherein both R^1 are optionally substituted C_{1-6} aliphatic groups.
14. The compound of claim 1, wherein both R^1 are hydrogen.
15. The compound of any one of claims 1 and 12 to 14, wherein R^2 is $-Cl$.
16. The compound of any one of claims 1 and 12 to 14, wherein R^2 is $-F$.
17. The compound of any one of claims 1 and 12 to 16, wherein R^3 is $-CF_3$.
18. The compound of any one of claims 1 and 12 to 16, wherein R^3 is $-OCF_3$.

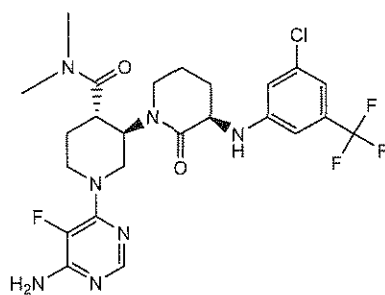
19. The compound of any one of claims 1 and 12 to 16, wherein R^3 is $-F$.
20. A compound selected from the group consisting of:



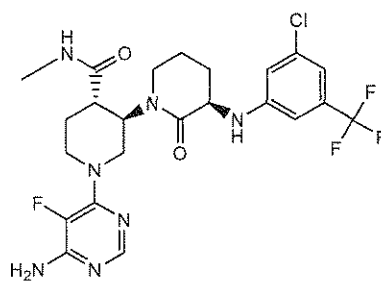
I-1



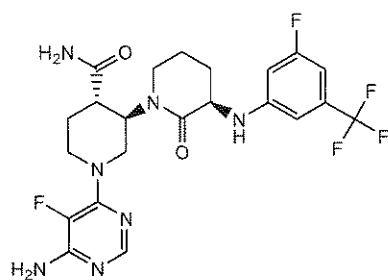
I-2



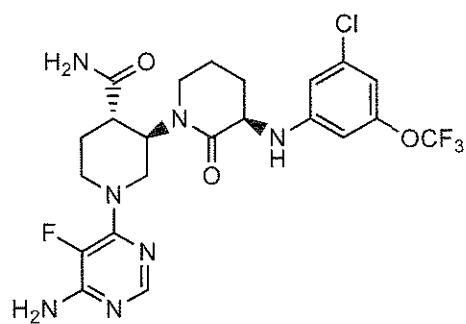
I-3



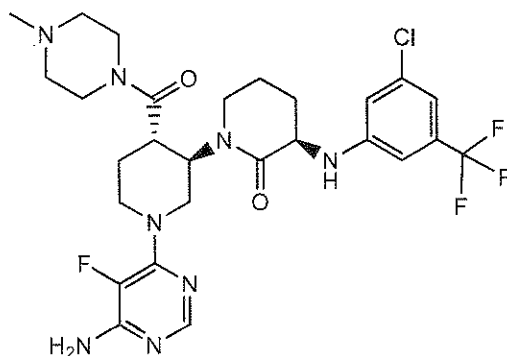
I-4



I-5



I-6



I-7

21. Use of a compound of any one of claims 1 to 20 or composition thereof, in the manufacture of a medicament for decreasing the enzymatic activity of Bruton's tyrosine kinase.
22. Use of a compound of any one of claims 1 to 20 or composition thereof, in the manufacture of a medicament for treating a disorder responsive to inhibition of Bruton's tyrosine kinase.
23. Use of a compound of any one of claims 1 to 20 or composition thereof, in the manufacture of a medicament for treating a disorder selected from the group consisting of autoimmune disorders, inflammatory disorders, and cancers.
24. The use of claim 23, wherein the disorder is rheumatoid arthritis.
25. The use of claim 23, wherein the disorder is systemic lupus erythematosus.
26. The use of claim 23, wherein the disorder is atopic dermatitis.
27. The use of claim 23, wherein the disorder is leukemia or lymphoma.
28. An *ex vivo* method of decreasing the enzymatic activity of Bruton's tyrosine kinase comprising contacting Bruton's tyrosine kinase with an effective amount of a compound of any one of claims 1-20 or a composition thereof.