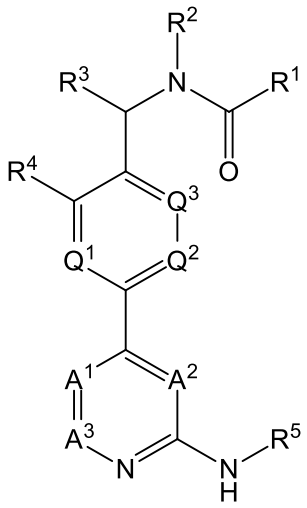
SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a compound of Formula **I'**:



I'

or a pharmaceutically acceptable salt, wherein:

one of A^1 and A^2 is C-R^6, and the other of A^1 and A^2 is selected from C-R^6 or N;

A^3 is selected from C-H or N, and is C-H when A^1 or A^2 is N;

Q^1 is selected from C-R^7 and N;

Q^2 is selected from C-R^7 and N;

Q^3 is selected from C-R^7 and N;

wherein at most one of Q^1, Q^2, and Q^3 is N;

R^1 is selected from $-N(R)_2$, phenyl, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl, wherein said phenyl, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms

selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl are optionally substituted with one or more R^{10};

R^2 is H or C_{1-6} aliphatic; or R^1 and R^2, together with their intervening atoms, form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, wherein said ring is optionally substituted with one or more R^{20};

R^3 is selected from H, halogen, -C(O)N$(R)_2$, -C(O)OR, -C(O)R, and C_{1-6} aliphatic, wherein the C_{1-6} aliphatic group is optionally substituted with hydroxyl;

each R^4 is independently selected from halogen, –NO_2, –CN, –OR, –SR, –N$(R)_2$, -C(O)R, -C(O)OR, –S(O)R, –$S(O)_2$R, –C(O)N$(R)_2$, -SO_2N$(R)_2$, -OC(O)R, –N(R)C(O)R, –N(R)C(O)OR, –N(R)SO_2R, -OC(O)N$(R)_2$, or C_{1-6} aliphatic, wherein said C_{1-6} aliphatic is optionally substituted with one or more R^{40};

or R^3 and R^4 together with their intervening atoms form fused Ring A selected from fused 5- to 7-membered monocyclic carbocycle, fused 5- to 7-membered monocyclic heterocycle having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said fused Ring A is optionally substituted with one or more R^{40};

R^5 is selected from H, -C(O)R, -C(O)OR, –S(O)R, –$S(O)_2$R, –C(O)N$(R)_2$, or C_{1-6} aliphatic, phenyl, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl, wherein said C_{1-6} aliphatic, phenyl, 3-

to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl, are optionally substituted with one or more R^{50};

each of R^6 and R^7 is independently selected from H, halogen, $–NO_2$, –CN, –OR, –SR, $–N(R)_2$, -C(O)R, -C(O)OR, –S(O)R, $–S(O)_2R$, $–C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, –N(R)C(O)R, –N(R)C(O)OR, $–N(R)SO_2R$, $-OC(O)N(R)_2$, or C_{1-6} aliphatic;

each R is independently hydrogen or C_{1-6} aliphatic, phenyl, 3- to 8-membered saturated or partially unsaturated carbocyclyl ring, 3- to 7- membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6} aliphatic, phenyl, 3- to 7-membered saturated or partially unsaturated carbocyclyl ring, 3- to 7- membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{50}; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said ring is optionally substituted with one or more R^{50};

each R^{10} is independently selected from halogen, $-OR^{10a}$, C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl

having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{15};

each R^{15} is independently selected from halogen and $-OR^{15a}$;

R^{10a} is C_{1-6}alkyl optionally substituted with halogen;

R^{15a} is C_{1-6}alkyl;

each R^{20} is independently selected from halogen, C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{15};

each R^{40} is independently selected from halogen, C_{1-6} alkyl, 4- to 6-membered monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, -C(O)H, $-N(R^{40a})_2$, $-N(R^{40a})C(O)(R^{40b})$, $-N(R^{40a})C(O)_2(R^{40a})$, $-OR^{40a}$, $-SR^{40a}$, and $-C(O)_2R^{40a}$, wherein said C_{1-6} alkyl group is optionally substituted with halogen or $–OR^{40a}$;

each R^{40a} is independently selected from H and C_{1-6}alkyl; or two R^{40a} groups on the same nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

each R^{40b} is independently selected from C_{2-6}alkenyl and 5- or 6-membered heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said 5- or 6-membered heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, is optionally substituted with one or more R^{45};

R^{45} is C_{1-6}alkyl;

each R^{50} is independently selected from C_{1-6}aliphatic, $-OR^{50a}$, $-N(R^{50a})_2$, $-C(O)N(R^{50a})_2$, $-C(O)_2R^{50a}$, oxo, 3- to 6-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 6-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 3- to 10-membered heterocyclyalkyl having 1-4 heteroatoms selected from

oxygen, nitrogen, or sulfur, wherein said C_{1-6}alkyl, 3- to 6-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 6-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 3- to 10-membered heterocyclyalkyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{55};

R^{50a} is selected from H and C_{1-6}alkyl;

each R^{55} is independently selected from 5- to 6-membered heterocyclyl having 1-2 heteroatoms selected from nitrogen, oxygen, or sulfur, C_{1-6}alkyl, $-OR^{55a}$, $-C(O)N(R^{55a})_2$, halogen, $-N(R^{55a})_2$, $-C(O)_2R^{55a}$, $-S(O)_2R^{55b}$, and $-S(O)_2(NR^{55a})_2$;

R^{55a} is selected from H and C_{1-6}alkyl, wherein said C_{1-6} alkyl is optionally substituted with halogen; and

R^{55b} is C_{1-6}alkyl.

[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

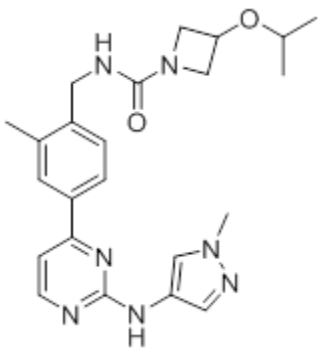
[0003c] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a composition thereof in the manufacture of a medicament for decreasing the enzymatic activity of Bruton's tyrosine kinase, wherein Bruton's tyrosine kinase is to be contacted with the compound or composition.

[0003d] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a composition thereof in the manufacture of a medicament for treating a disorder responsive to inhibition of Bruton’s tyrosine kinase.

[0003e] In a further aspect of the present disclosure, there is provided a use of a compound as 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.

[0003f] In another aspect of the present disclosure, there is provided a compound as disclosed herein or a composition thereof for use in therapy.

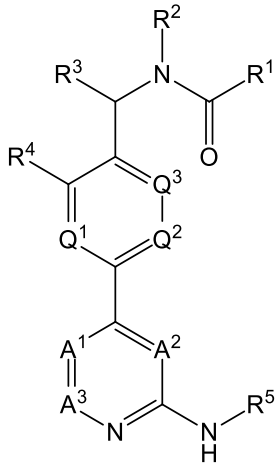
[0003g] In a further aspect of the present disclosure, there is provided a compound of formula **I-21**:



I-21,

or a pharmaceutically acceptable salt thereof.

[0004] In certain examples, the present disclosure provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, Q^1, Q^2, Q^3, A^1, A^2, and A^3 is as defined and described in classes and subclasses herein.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0005] In some embodiments, the present invention provides a compound of formula **I**:

each R^{40} is independently selected from halogen, C_{1-6} alkyl, 4- to 6-membered monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, -C(O)H, $-N(R^{40a})_2$, $-N(R^{40a})C(O)(R^{40b})$, $-N(R^{40a})C(O)_2(R^{40a})$, $-OR^{40a}$, $-SR^{40a}$, and $-C(O)_2R^{40a}$, wherein said C_{1-6} alkyl group is optionally substituted with halogen or $–OR^{40a}$;

each R^{40a} is independently selected from H and C_{1-6}alkyl; or two R^{40a} groups on the same nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

each R^{40b} is independently selected from C_{2-6}alkenyl and 5- or 6-membered heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said 5- or 6-membered heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, is optionally substituted with one or more R^{45};

R^{45} is C_{1-6}alkyl;

each R^{50} is independently selected from C_{1-6}aliphatic, $-OR^{50a}$, $-N(R^{50a})_2$, $-C(O)N(R^{50a})_2$, $-C(O)_2R^{50a}$, oxo, 3- to 6-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 6-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 3- to 10-membered heterocyclyalkyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6}alkyl, 3- to 6-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 6-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 3- to 10-membered heterocyclyalkyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{55};

R^{50a} is selected from H and C_{1-6}alkyl;

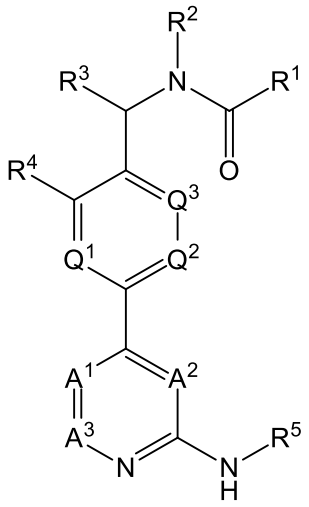
each R^{55} is independently selected from 5- to 6-membered heterocyclyl having 1-2 heteroatoms selected from nitrogen, oxygen, or sulfur, C_{1-6}alkyl, $-OR^{55a}$, $-C(O)N(R^{55a})_2$, halogen, $-N(R^{55a})_2$, $-C(O)_2R^{55a}$, $-S(O)_2R^{55b}$, and $-S(O)_2(NR^{55a})_2$;

R^{55a} is selected from H and C_{1-6}alkyl, wherein said C_{1-6} alkyl is optionally substituted with halogen; and

CLAIMS

What is claimed is:

1. A compound of Formula **I'**:



I'

or a pharmaceutically acceptable salt, wherein:

one of A^1 and A^2 is C-R^6, and the other of A^1 and A^2 is selected from C-R^6 or N;

A^3 is selected from C-H or N, and is C-H when A^1 or A^2 is N;

Q^1 is selected from C-R^7 and N;

Q^2 is selected from C-R^7 and N;

Q^3 is selected from C-R^7 and N;

wherein at most one of Q^1, Q^2, and Q^3 is N;

R^1 is selected from $–N(R)_2$, phenyl, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms

selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl, wherein said phenyl, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl are optionally substituted with one or more R^{10};

R^2 is H or C_{1-6} aliphatic;

or R^1 and R^2, together with their intervening atoms, form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, wherein said ring is optionally substituted with one or more R^{20};

R^3 is selected from H, halogen, -C(O)N(R)$_2$, -C(O)OR, -C(O)R, and C_{1-6} aliphatic, wherein the C_{1-6} aliphatic group is optionally substituted with hydroxyl;

each R^4 is independently selected from halogen, –NO$_2$, –CN, –OR, –SR, –N(R)$_2$, -C(O)R, -C(O)OR, –S(O)R, –S(O)$_2$R, –C(O)N(R)$_2$, -SO$_2$N(R)$_2$, -OC(O)R, –N(R)C(O)R, –N(R)C(O)OR, –N(R)SO$_2$R, -OC(O)N(R)$_2$, or C_{1-6} aliphatic, wherein said C_{1-6} aliphatic is optionally substituted with one or more R^{40};

or R^3 and R^4 together with their intervening atoms form fused Ring A selected from fused 5- to 7-membered monocyclic carbocycle, fused 5- to 7-membered monocyclic heterocycle having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said fused Ring A is optionally substituted with one or more R^{40};

R^5 is selected from H, -C(O)R, -C(O)OR, –S(O)R, –S(O)$_2$R, –C(O)N(R)$_2$, or C_{1-6} aliphatic, phenyl, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4

heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl, wherein said C_{1-6} aliphatic, phenyl, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, or 8- to 10-membered bicyclic aryl, are optionally substituted with one or more R^{50};

each of R^6 and R^7 is independently selected from H, halogen, $–NO_2$, –CN, –OR, –SR, $–N(R)_2$, -C(O)R, -C(O)OR, –S(O)R, $–S(O)_2R$, $–C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, –N(R)C(O)R, –N(R)C(O)OR, $–N(R)SO_2R$, $-OC(O)N(R)_2$, or C_{1-6} aliphatic;

each R is independently hydrogen or C_{1-6} aliphatic, phenyl, 3- to 8-membered saturated or partially unsaturated carbocyclyl ring, 3- to 7- membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6} aliphatic, phenyl, 3- to 7-membered saturated or partially unsaturated carbocyclyl ring, 3- to 7- membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{50}; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said ring is optionally substituted with one or more R^{50};

each R^{10} is independently selected from halogen, -OR^{10a}, C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{15};

each R^{15} is independently selected from halogen and -OR^{15a};

R^{10a} is C_{1-6}alkyl optionally substituted with halogen;

R^{15a} is C_{1-6}alkyl;

each R^{20} is independently selected from halogen, C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6}aliphatic, 3- to 5-membered saturated or partially unsaturated carbocyclyl, 3- to 5-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{15};

each R^{40} is independently selected from halogen, C_{1-6} alkyl, 4- to 6-membered monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, -C(O)H, -$N(R^{40a})_2$, -$N(R^{40a})C(O)(R^{40b})$, -$N(R^{40a})C(O)_2(R^{40a})$, -$OR^{40a}$, -$SR^{40a}$, and -$C(O)_2R^{40a}$, wherein said C_{1-6} alkyl group is optionally substituted with halogen or –OR^{40a};

each R^{40a} is independently selected from H and C_{1-6}alkyl; or two R^{40a} groups on the same nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

each R^{40b} is independently selected from C_{2-6}alkenyl and 5- or 6-membered heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said 5- or 6-membered heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, is optionally substituted with one or more R^{45};

R^{45} is C_{1-6}alkyl;

each R^{50} is independently selected from

C_{1-6}aliphatic, $-OR^{50a}$, $-N(R^{50a})_2$, $-C(O)N(R^{50a})_2$, $-C(O)_2R^{50a}$, oxo, 3- to 6-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 6-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 3- to 10-membered heterocyclyalkyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein said C_{1-6}alkyl, 3- to 6-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 6-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 3- to 10-membered heterocyclyalkyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, are optionally substituted with one or more R^{55};

R^{50a} is selected from H and C_{1-6}alkyl;

each R^{55} is independently selected from 5- to 6-membered heterocyclyl having 1-2 heteroatoms selected from nitrogen, oxygen, or sulfur, C_{1-6}alkyl, $-OR^{55a}$, $-C(O)N(R^{55a})_2$, halogen, $-N(R^{55a})_2$, $-C(O)_2R^{55a}$, $-S(O)_2R^{55b}$, and $-S(O)_2(NR^{55a})_2$;

R^{55a} is selected from H and C_{1-6}alkyl, wherein said C_{1-6} alkyl is optionally substituted with halogen; and

R^{55b} is C_{1-6}alkyl.

2. The compound of claim 1, wherein R^1 is selected from 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, phenyl, or 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein R^1 is optionally substituted with one or more R^{10}.

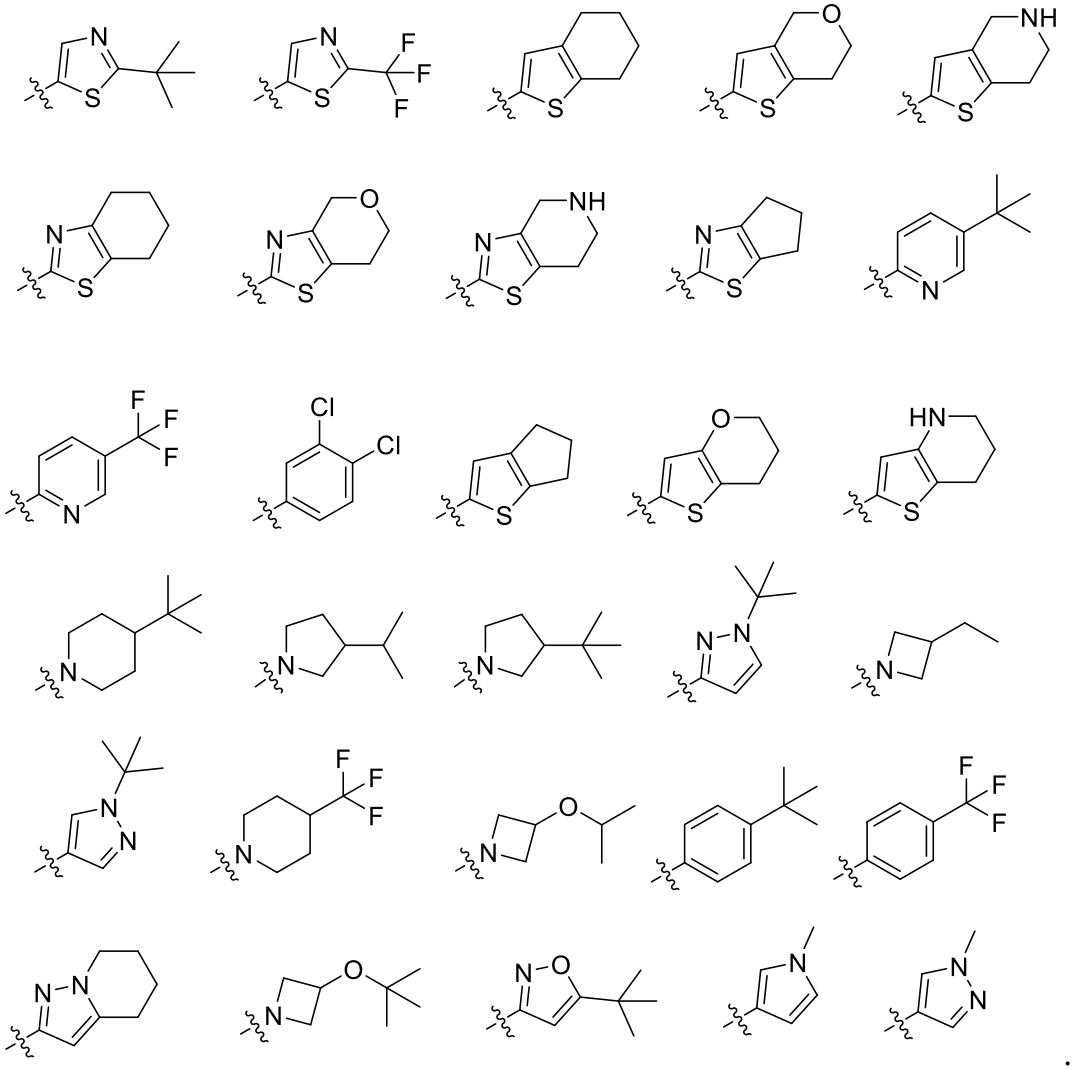
3. The compound claim 2, wherein R^1 is selected from thiazolyl, pyrazolyl, isoxazolyl, or thiophenyl, wherein R^1 is optionally substituted with one or more R^{10}.

4. The compound of claim 3, wherein R^{10} is C_{1-6}aliphatic optionally substituted with one or more R^{15}, wherein R^{15} is halogen.

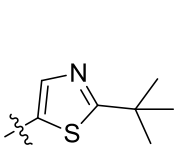
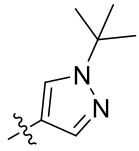
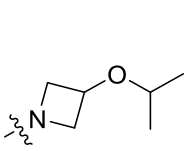
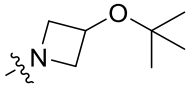
5. The compound of claim 2, wherein R^1 is selected from pyridyl, piperidinyl, or azetidinyl, wherein R^1 is optionally substituted with one or more R^{10}.

6. The compound of claim 5, wherein R^{10} is -OR^{10a}, or C_{1-6}aliphatic, wherein the C_{1-6}aliphatic is optionally substituted with one or more R^{15}, wherein R^{15} is halogen.

7. The compound of any one of the preceding claims, wherein R^1 is selected from:



.

8. The compound of claim 6, wherein R^1 is , , , or .

9. The compound of claim 1, wherein R^1 and R^2, together with their intervening atoms, form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, or 7- to 10-membered bicyclic heterocyclyl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein the ring is optionally substituted with one or more R^{20}.

10. The compound of claim 9, wherein each R^{20} is independently selected from C_{1-6} aliphatic or 3- to 5-membered saturated or partially unsaturated carbocyclyl.

11. The compound of any one of the preceding claims, wherein R^3 is hydrogen.

12. The compound of any one of the preceding claims, wherein R^4 is halogen.

13. The compound of any one claims 1-11, wherein R^4 is C_{1-6} aliphatic optionally substituted with one or more R^{40}, wherein R^{40} is halogen.

14. The compound of any one claims 1-11 or 13, wherein R^4 is methyl.

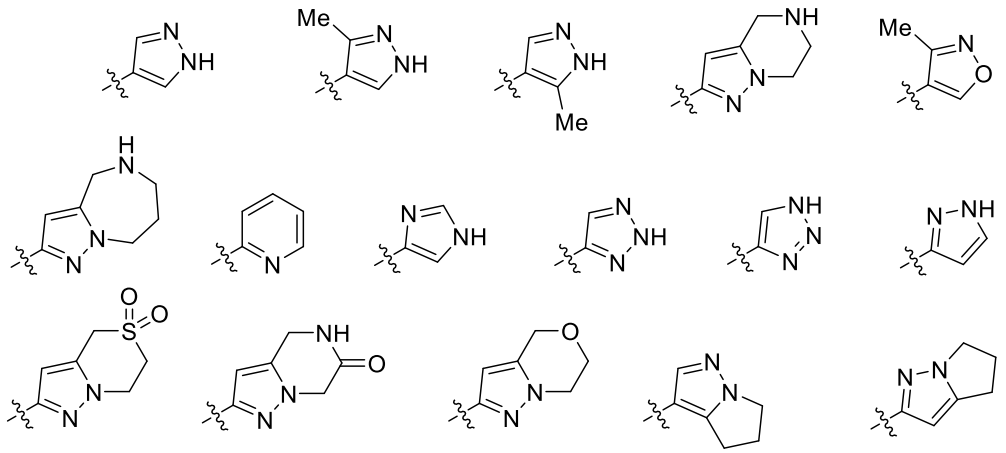
15. The compound of any one of claims 1-10, wherein R^3 and R^4, together with their intervening atoms, form fused Ring A selected from fused 5- to 7-membered monocyclic carbocycle, or fused 5- to 7-membered heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

16. The compound of any one of the preceding claims, wherein R^5 is selected from hydrogen, -C(O)R, or 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein the 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur is optionally substituted with one or more R^{50}.

17. The compound of claim 16, wherein R^5 is hydrogen.

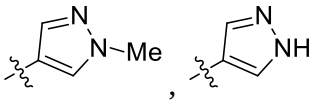
18. The compound of claim 16, wherein R^5 is selected from pyrazolyl, imidazolyl, isoxazolyl, triazolyl, tetrazolyl, thiadiazolyl, or pyridyl, wherein R^5 is optionally substituted with one or more R^{50}.

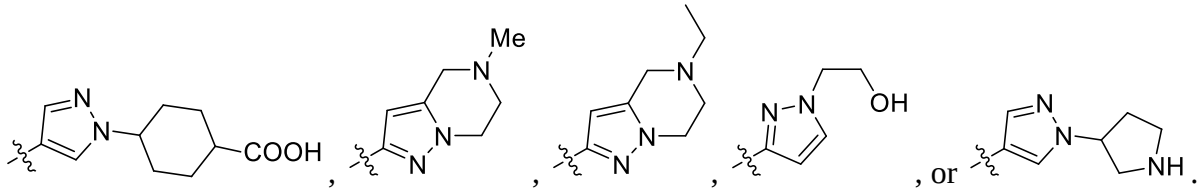
19. The compound of claim 1, wherein R^5 is selected from:



wherein each group is optionally substituted with one or more R^{50}.

20. The compound of claim 19, wherein each R^{50} is independently selected from methyl, ethyl, isopropyl, $-C(O)_2R^{50a}$, $-C(CH_3)_2C(O)N(R^{55a})_2$, $-(CH_2)_2OH$, $-(CH_2)_2OMe$, $-(CH_2)_2NH_2$, $-CH_2CHOHCH_2NH_2$, $-CH_2CHNH_2COOH$, $-CH_2CHNH_2CH_2OH$, $-CH_2$-morpholinyl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, cyclobutyl, piperidinyl, or cyclohexyl, wherein said tetrahydropyranyl, azetidinyl, pyrrolidinyl, cyclobutyl, piperidinyl, piperizinyl, or cyclohexyl may be substituted with $C_{1\text{-}6}$alkyl, halogen, hydroxyl, or $C(O)_2R^{55a}$.

21. The compound of claim 19, wherein R^5 is , ,



22. The compound of any one of the preceding claims, wherein each R^6 is independently selected from hydrogen, halogen, or $C_{1\text{-}6}$ aliphatic.

23. The compound of claim 22, wherein each R^6 is independently selected from hydrogen, fluoro, or methyl.

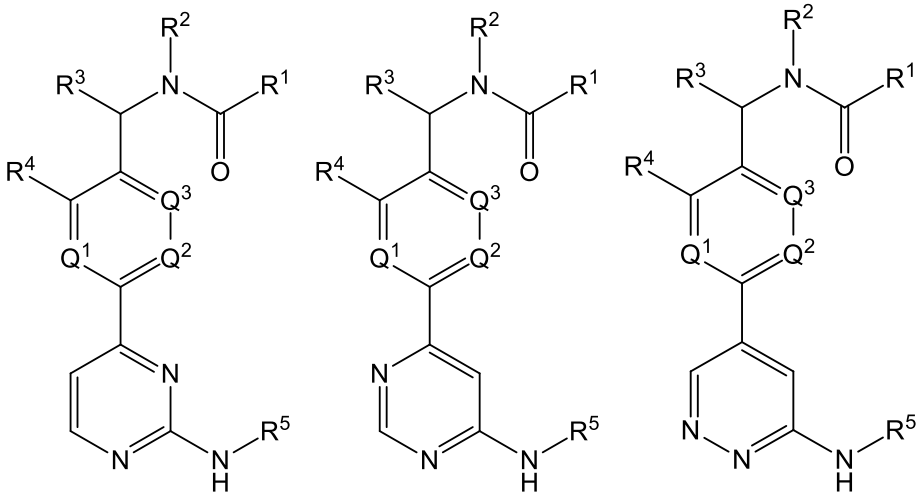
24. The compound of claim 22, wherein each R^6 is hydrogen.

25. The compound of any one of the preceding claims, wherein each R^7 is independently selected from hydrogen or halogen.

26. The compound of claim 25, wherein each R^7 is hydrogen.

27. The compound of claim 25, wherein R^4 is halogen, one R^7 is halogen, and other R^7 groups are hydrogen.

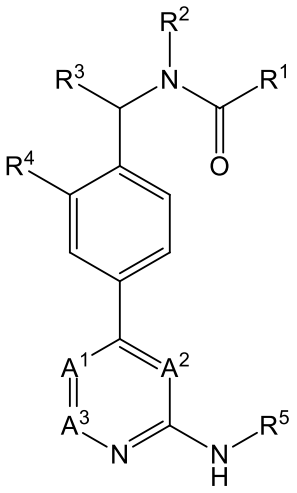
28. The compound of any one of the preceding claims, wherein the compound is of formula **II-a**, **II-b**, or **II-c**:



II-a **II-b** **II-c**

or a pharmaceutically acceptable salt thereof.

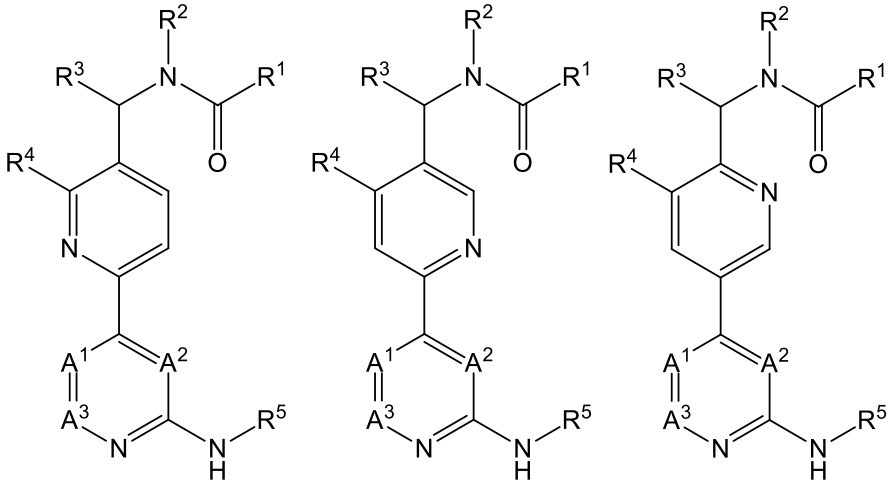
29. The compound of any one of claims 1-27, wherein the compound is of formula **III**:



III

or a pharmaceutically acceptable salt thereof.

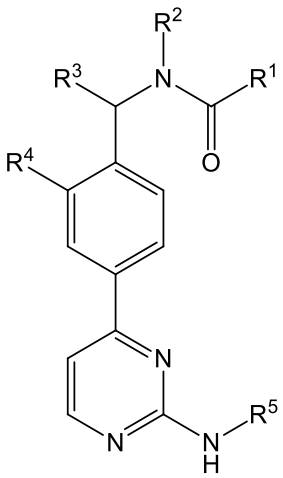
30. The compound of any one of claims 1-27, wherein the compound is of formula **IV-a**, **IV-b**, or **IV-c**:



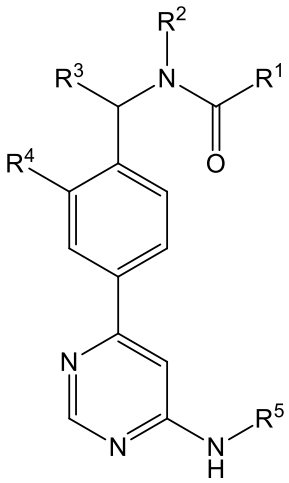
IV-a **IV-b** **IV-c**

or a pharmaceutically acceptable salt thereof.

31. The compound of any one of claims 1-27, wherein the compound is of formula **V-a** or **V-b**:



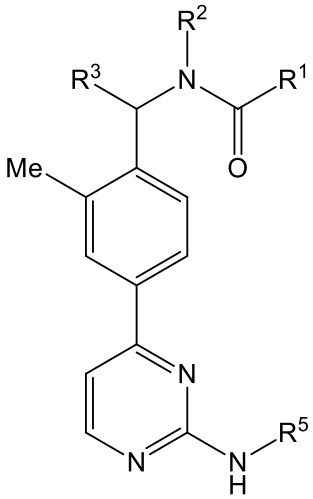
V-a



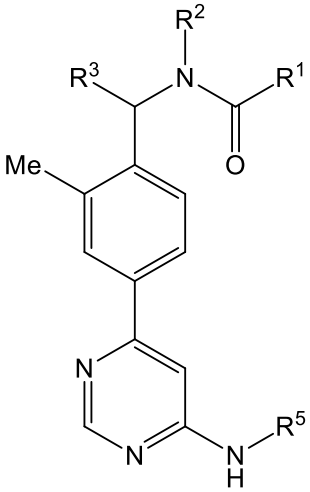
V-b

or a pharmaceutically acceptable salt thereof.

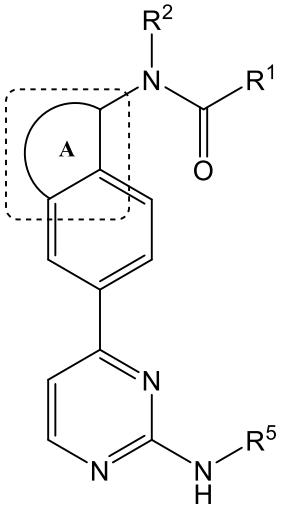
32. The compound of any one of claims 1-27, wherein the compound is of formula **VI-a**, **VI-b**, **VI-c**, or **VI-d**:



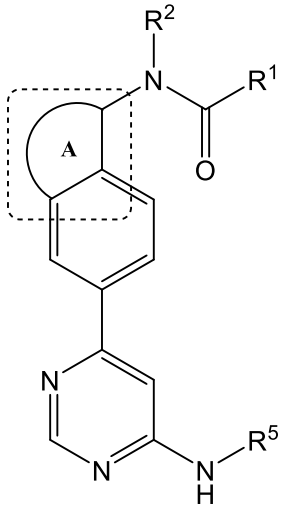
VI-a



VI-b



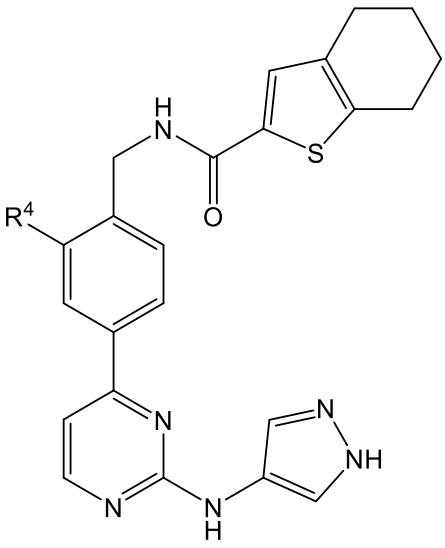
VI-c



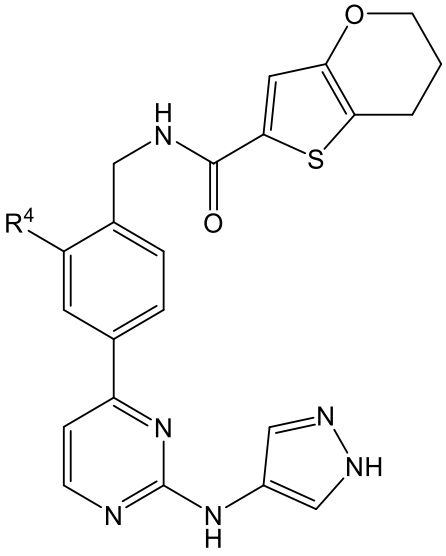
VI-d

or a pharmaceutically acceptable salt thereof.

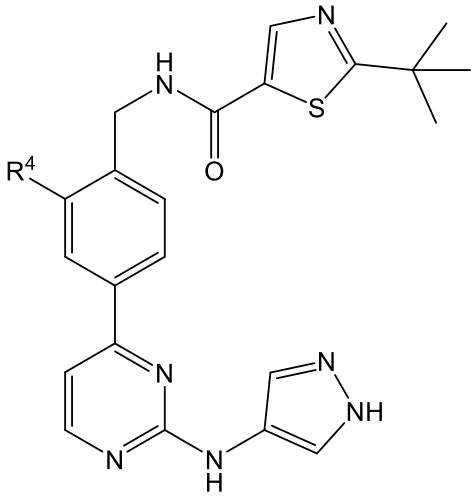
33. The compound of any one of claims 1-27, wherein the compound is of formula **VII-a**, **VII-b**, **VII-c**, or **VII-d**:



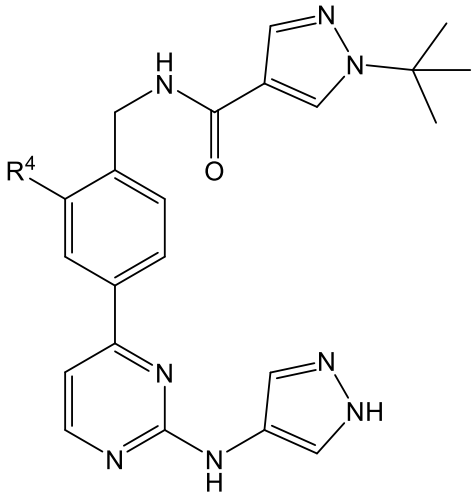
VII-a



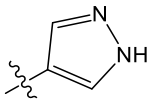
VII-b



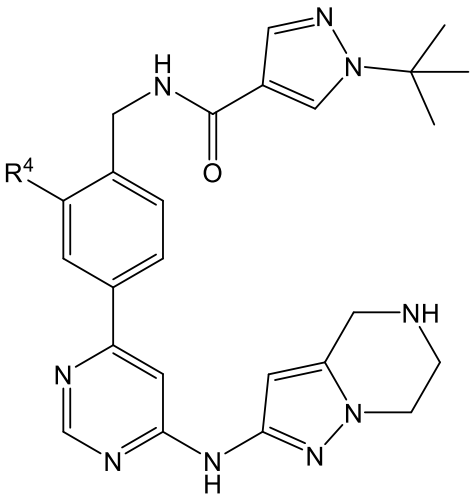
VII-c



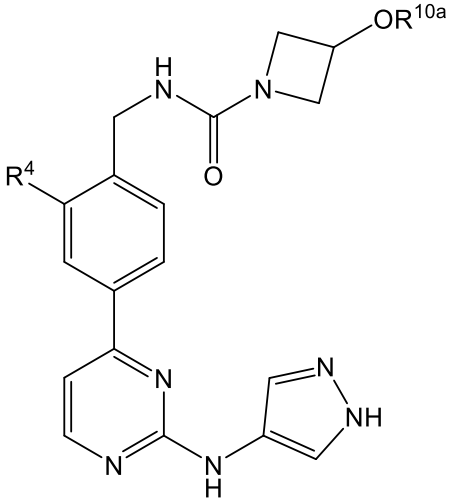
VII-d

or a pharmaceutically acceptable salt thereof, wherein the  moiety is optionally substituted with one or more R^{50}.

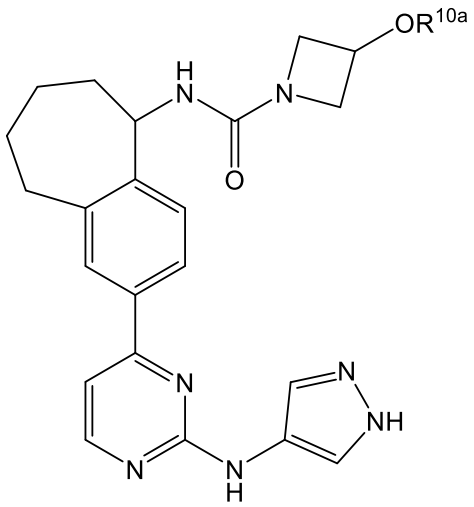
34. The compound of any one of claims 1-27, wherein the compound is of formula **VIII-a**, **VIII-b**, or **VIII-c**:



VIII-a

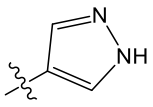
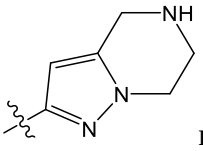


VIII-b



VIII-c

or a pharmaceutically acceptable salt thereof, wherein:

R^{10a} is C_{1-6} alkyl, R^4 is methyl or CF_3, and the  and  moieties are optionally substituted with one or more R^{50}.

35. The compound of any one of the preceding claims, wherein the compound is selected from compounds I-1 through I-360 as depicted in Examples 1-238.

36. A pharmaceutical composition comprising a compound of any one of claims 1-35 and a pharmaceutically acceptable excipient.

37. Use of a compound of any one of claims 1-35 or a composition thereof in the manufacture of a medicament for decreasing the enzymatic activity of Bruton's tyrosine kinase, wherein Bruton's tyrosine kinase is to be contacted with the compound or composition.

38. Use of a compound of any one of claims 1-35 or a composition thereof in the manufacture of a medicament for treating a disorder responsive to inhibition of Bruton's tyrosine kinase.

39. Use of a compound of any one of claims 1-35 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.

40. The use of claim 39, wherein the disorder is rheumatoid arthritis.

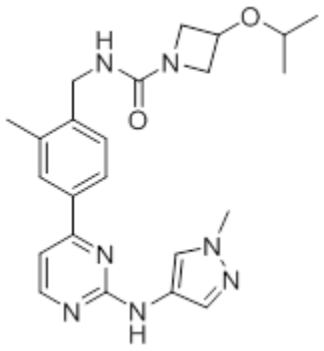
41. The use of claim 39, wherein the disorder is systemic lupus erythematosus.

42. The use of claim 39, wherein the disorder is atopic dermatitis.

43. The use of claim 39, wherein the disorder is leukemia or lymphoma.

44. A compound of any one of claims 1-35 or a composition thereof for use in therapy.

45. A compound of formula **I-21**:



I-21,

or a pharmaceutically acceptable salt thereof.