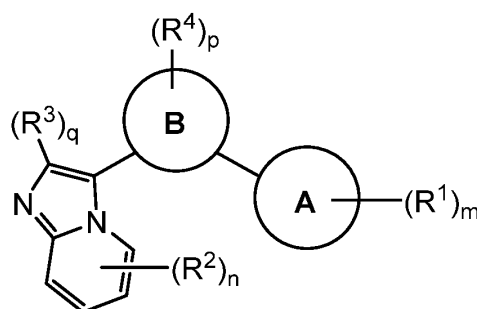


CLAIMS

We claim:

1. A compound of formula I:



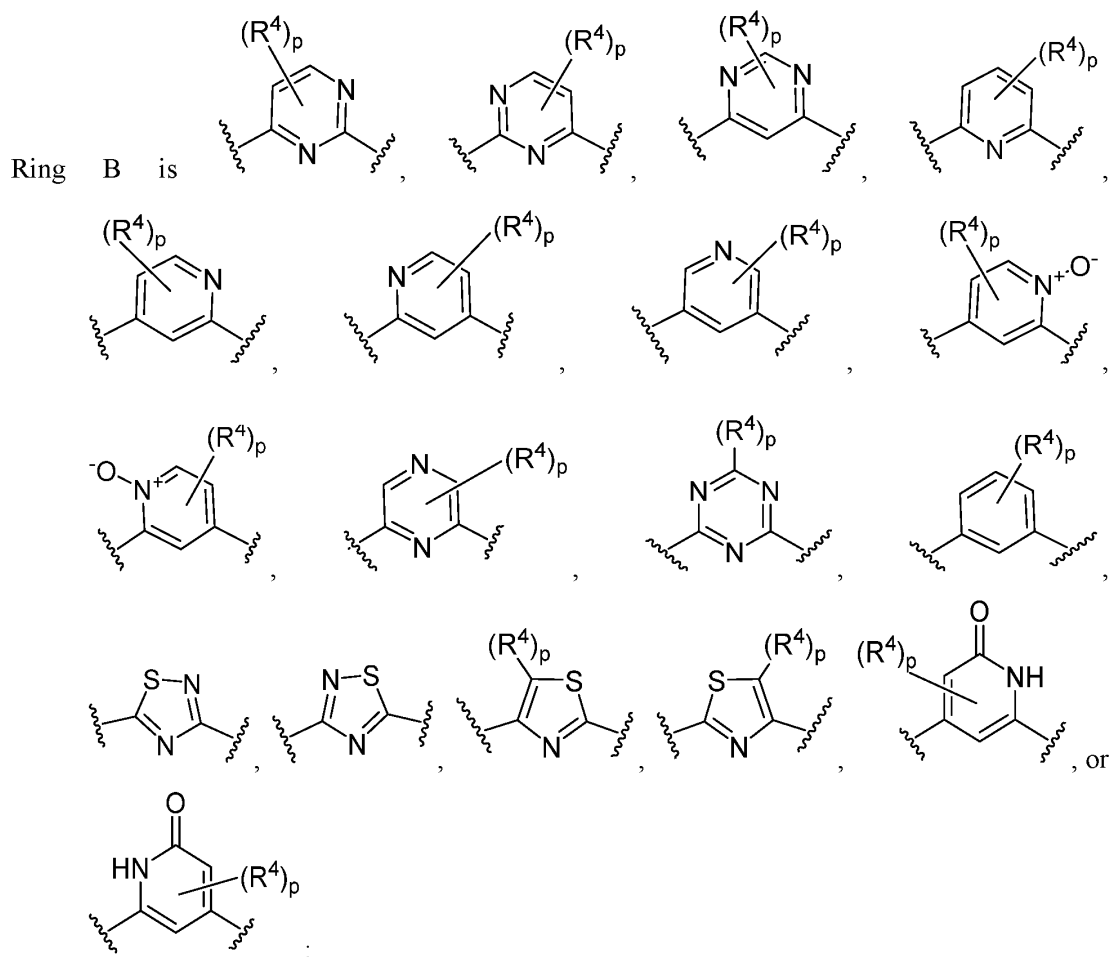
I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur optionally fused to a 5-6 membered aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-12 membered partially unsaturated spirocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-12 membered partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-12 membered partially unsaturated bridged bicyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

Het, wherein Het is a 4-8 membered saturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-12 membered saturated spirocyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-12 membered saturated bicyclic heterocyclic ring

having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-12 membered saturated bridged bicyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;



each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

two R groups are optionally taken together to form a bivalent C₂₋₄ alkylene chain;

two R groups are optionally taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

each R' is independently hydrogen or a C₁₋₃ aliphatic group optionally substituted with halogen;

each of R¹ is independently hydrogen, halogen, -CN, -NO₂, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NRS(O)₂R, -C(O)N=S(O)R₂, -NR₂, -NRC(O)R, -NRC(O)NR₂, -NRC(O)OR, -NRS(O)₂R, -NRS(O)₂NR₂, -OR, -ON(R)SO₂R, -P(O)R₂, -SR, -S(O)R, -S(O)₂R, -S(O)(NH)R, -S(O)₂N(R)₂, -S(NH₂)₂(O)OH, -N=S(O)R₂, -CH₃, -CH₂OH, -CH₂NHSO₂CH₃, -CD₃, -CD₂NRS(O)₂R, or R; or:

two R¹ groups are optionally taken together to form =O or =NH; or

two R¹ groups are optionally taken together to form a bivalent C₂₋₄ alkylene chain;

each of R² is independently hydrogen, halogen, -CN, -C(O)N(R')₂, -OR', -N(R')₂, -S(O)₂R, -S(O)₂N(R)₂, -O-phenyl, or an optionally substituted group selected from C₁₋₃ aliphatic, phenyl, 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 4-8 membered saturated monocyclic heterocycle having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R³ is hydrogen, halogen, -CN, -OR', -N(R')₂, or an optionally substituted group selected from C₁₋₃ aliphatic, phenyl, or a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R⁴ is hydrogen, halogen, -CN, -OR, -N=S(O)R₂, -N(R)₂, or an optionally substituted group selected from C₁₋₃ aliphatic, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-12 membered saturated or partially unsaturated spirocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

m is 0, 1, 2, 3, 4 or 5;

n is 0, 1, or 2;

p is 0 or 1; and

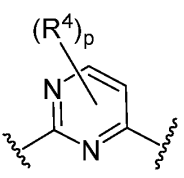
q is 0 or 1.

2. The compound of claim 1, wherein Ring A is Het.
3. The compound of claim 2, wherein Het is a 4-8 membered saturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-12 membered saturated spirocyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-12 membered saturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

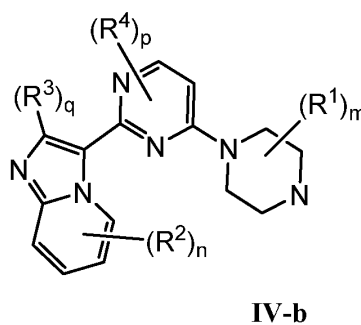
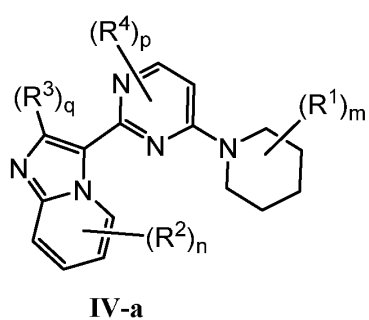
- [illegible]

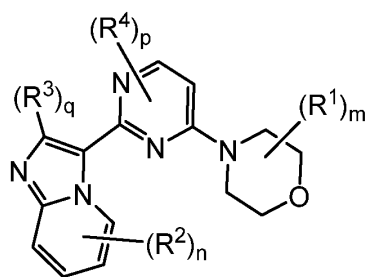
5. The compound of claim 1, wherein each of R¹ is independently hydrogen, halogen, -CN, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NRS(O)₂R, -C(O)N=S(O)R₂, -NR₂, -NRC(O)R, -NRC(O)NR₂, -NRC(O)OR, -NRS(O)₂R, -NRS(O)₂NR₂, -OR, -ON(R)SO₂R, -P(O)R₂, -SR, -S(O)R, -S(O)₂R, -S(O)(NH)R, -S(O)₂N(R)₂, -S(NH₂)₂(O)OH, -N=S(O)R₂, -CH₃, -CH₂OH, -CH₂NHSO₂CH₃, -CD₃, -CD₂NRS(O)₂R, or R.

6. The compound of claim 1, wherein each of R^2 is independently hydrogen, halogen, $-CN$, $-C(O)N(R')_2$, $-OR'$, $-N(R')_2$, or an optionally substituted group selected from C_{1-3} aliphatic, or a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
7. The compound of claim 1, wherein R^3 is hydrogen, halogen, $-CN$, $-OR'$, $-N(R')_2$, or an optionally substituted group selected from C_{1-3} aliphatic, or a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
8. The compound of claim 1, wherein R^4 is hydrogen, halogen, $-CN$, $-OR$, $-N(R)_2$, or an optionally substituted group selected from C_{1-3} aliphatic, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-12 membered saturated or partially unsaturated spirocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

9. The compound of claim 1, wherein Ring B is .

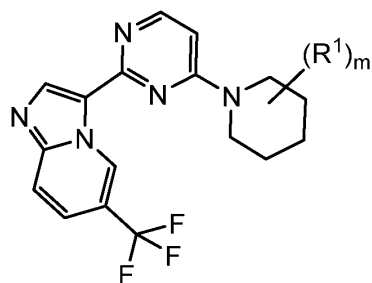
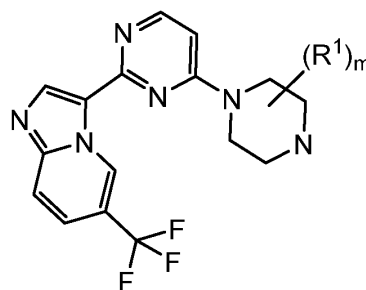
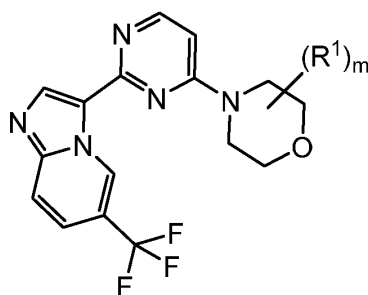
10. The compound of claim 9, of one of formula **IV-a**, **IV-b**, or **IV-c**:



**IV-c**

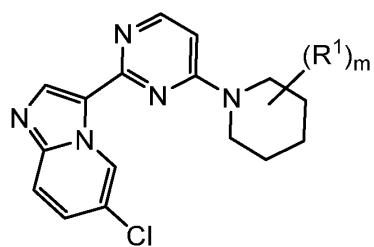
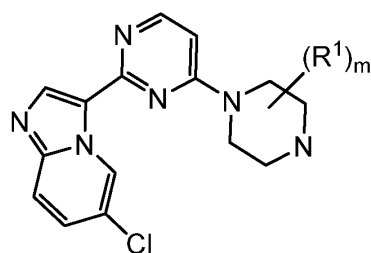
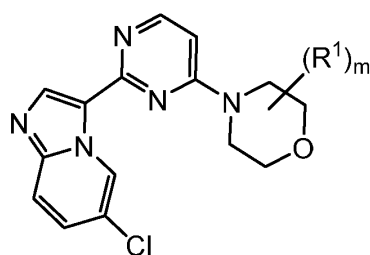
or a pharmaceutically acceptable salt thereof.

11. The compound of claim 9, of one of formula **XIII-a**, **XIII-a**, or **XIII-c**:

**XIII-a****XIII-a****XIII-c**

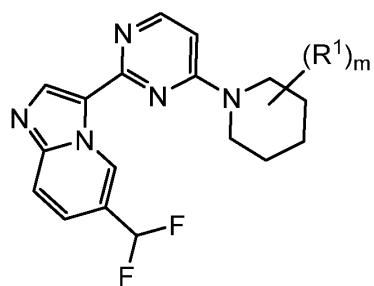
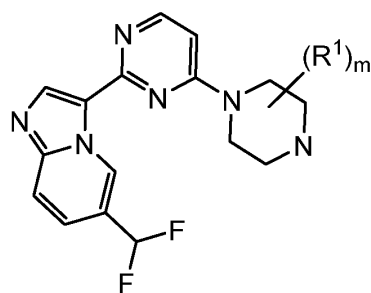
or a pharmaceutically acceptable salt thereof.

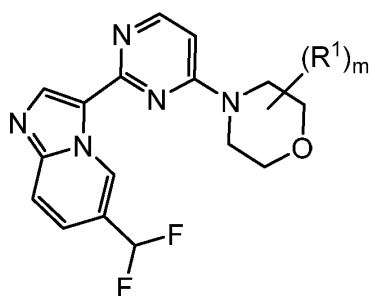
12. The compound of claim 9, of one of formula **XIV-a**, **XIV-a**, or **XIV-c**:

**XIV-a****XIV-b****XIV-c**

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 9, of one of formula **XV-a**, **XV-a**, or **XV-c**:

**XV-a****XV-b**

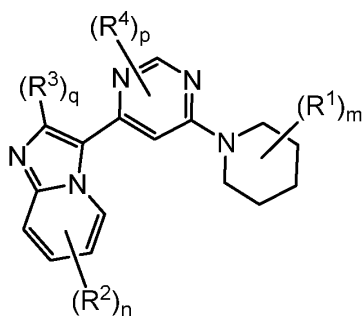
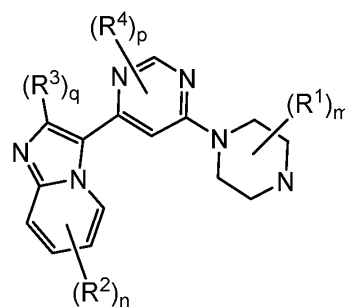
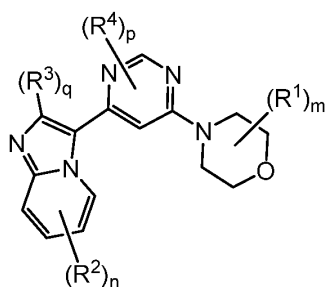
**XV-c**

or a pharmaceutically acceptable salt thereof.

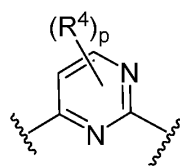


14. The compound of claim 1, wherein Ring B is

15. The compound of claim 14, of one of formula **VI-a**, **VI-b**, or **VI-c**:

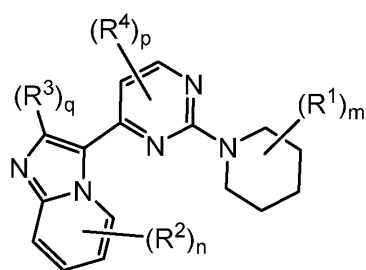
**VI-a****VI-b****VI-c**

or a pharmaceutically acceptable salt thereof.

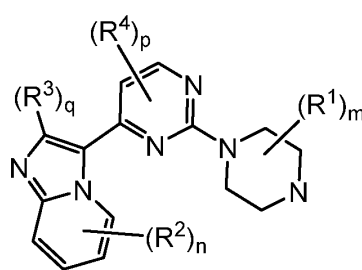


16. The compound of claim 1, wherein Ring B is

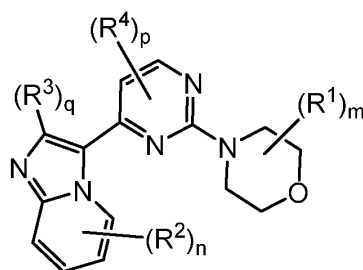
17. The compound of claim 16, of one of formula **XII-a**, **XII-b**, or **XII-c**:



XII-a



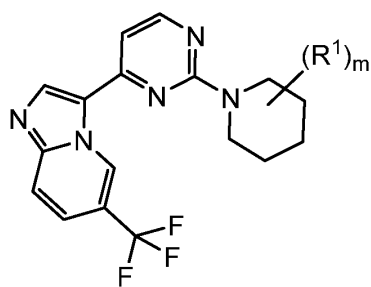
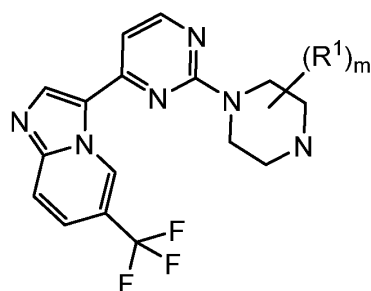
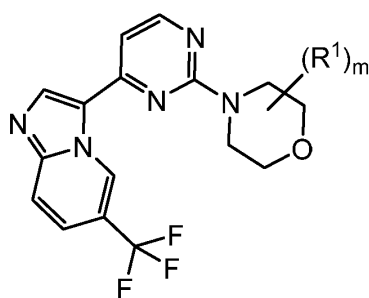
XII-b



XII-c

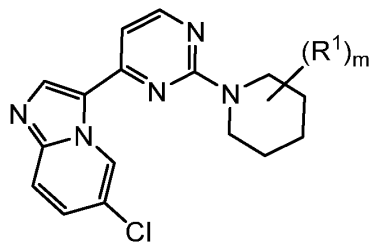
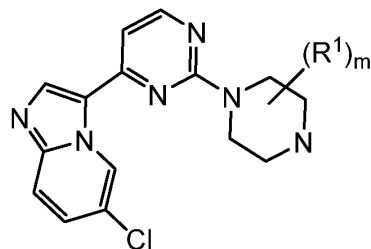
or a pharmaceutically acceptable salt thereof.

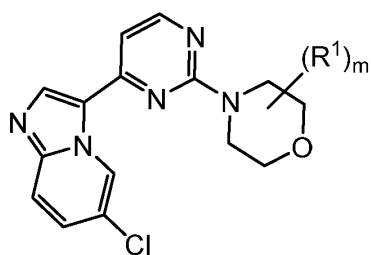
18. The compound of claim 16, of one of formula **XVI-a**, **XVI-b**, or **XVI-c**:

**XVI-a****XVI-b****XVI-c**

or a pharmaceutically acceptable salt thereof.

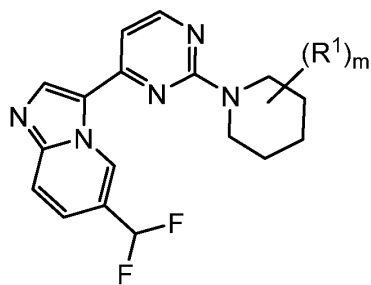
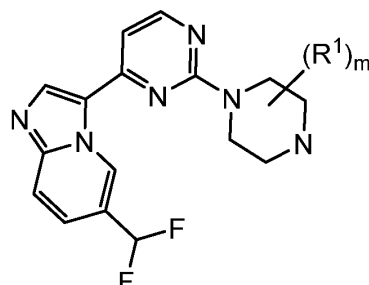
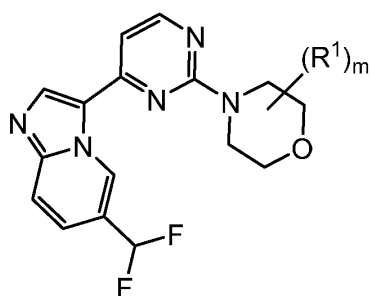
19. The compound of claim 16, of one of formula **XVII-a**, **XVII-b**, or **XVII-c**:

**XVII-a****XVII-b**

**XVII-c**

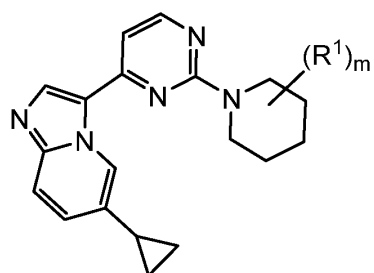
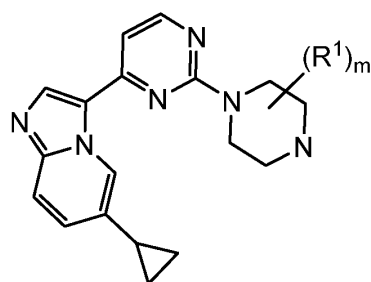
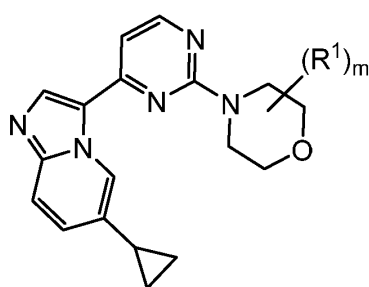
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 16, of one of formula **XVIII-a**, **XVIII-b**, or **XVIII-c**:

**XVIII-a****XVIII-b****XVIII-c**

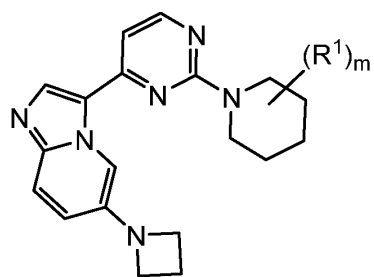
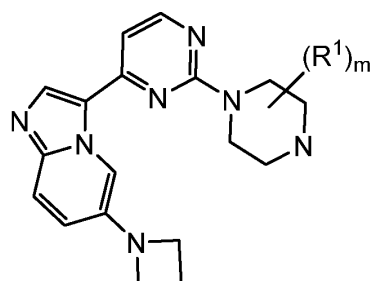
or a pharmaceutically acceptable salt thereof.

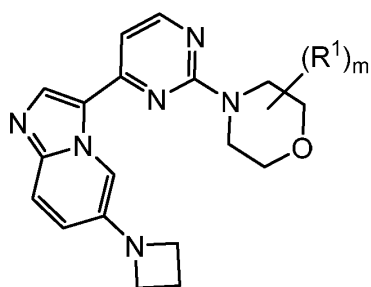
21. The compound of claim 16, of one of formula **XIX-a**, **XIX-b**, or **XIX-c**:

**XIX-a****XIX-b****XIX-c**

or a pharmaceutically acceptable salt thereof.

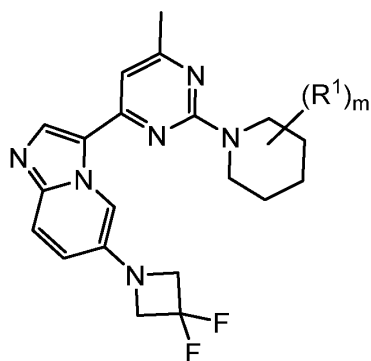
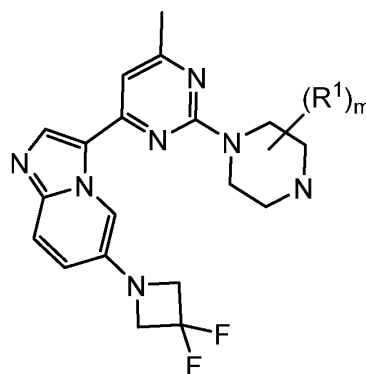
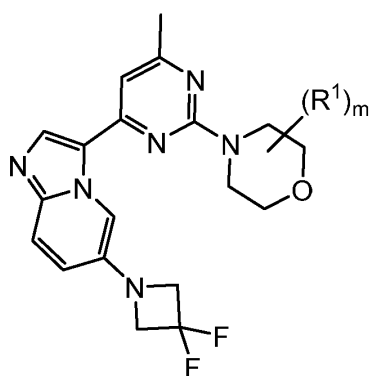
22. The compound of claim 16, of one of formula **XX-a**, **XX-b**, or **XX-c**:

**XX-a****XX-b**

**XX-c**

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 16, of one of formula **XXI-a**, **XXI-b**, or **XXI-c**:

**XXI-a****XXI-b****XXI-c**

or a pharmaceutically acceptable salt thereof.

24. The compound of any one of claims 1 to 23, wherein m is 1, 2, 3, 4 or 5, in particular 1, 2 or 3.
25. The compound of claim 1 wherein the compound is selected from those depicted in **Table 1**.
26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 25, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
27. A method of inhibiting GCN2 in a patient or biological sample comprising administering to said patient, or contacting said biological sample with a compound according to any one of claims 1 to 25, or a pharmaceutical composition thereof.
28. A method of treating a GCN2-mediated disorder, disease, or condition in a patient comprising administering to said patient a compound according to any one of claims 1 to 25, or a pharmaceutical composition thereof.
29. The method of claim 28, wherein the GCN2-mediated disorder, disease or condition is selected from the group consisting of inflammatory conditions, immunological conditions, autoimmune conditions, allergic conditions, rheumatic conditions, thrombotic conditions, cancer, infections, neurodegenerative diseases, degenerative diseases, neuroinflammatory diseases, cardiovascular diseases, and metabolic conditions.
30. The method of claim 29, wherein the cancer is selected the group consisting of a solid tumor, wherein the solid tumor originates from the group of tumors of the epithelium, the bladder, the stomach, the kidneys, of head and neck, the esophagus, the cervix, the thyroid, the intestine, the liver, the brain, the prostate, the uro-genital tract, the lymphatic system, the stomach, the larynx, the bones, including chondrosarcoma and Ewing sarcoma, germ cells, including embryonal tissue tumors, and/or the lung, from the group of monocytic leukemia, lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, glioblastomas, neurofibroma,

angiosarcoma, breast carcinoma and /or maligna melanoma, and a tumor of the blood and immune system.

31. The method of claim 29, wherein the autoimmune condition is rheumatoid arthritis, systemic lupus, multiple sclerosis, psoriasis, Sjögrens syndrome or transplant organ rejection.

32. The method of claim 29, wherein the metabolic condition is diabetes.

33. The method of claim 29, wherein the degenerative disease is osteoarthritis.

34. The method of claim 29, wherein the inflammatory condition is asthma, inflammatory bowel disease, or giant cell arteritis.

35. The method of claim 29, wherein the cardiovascular disease is an ischemic injury.

36. The method of claim 29, wherein the neurodegenerative disease is Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis-Dutch Type, cerebral amyloid angiopathy, Creutzfeldt-Jakob disease, frontotemporal dementias, Huntington's disease, or Parkinson's disease.

37. The method of claim 29, wherein the infection is caused by leishmania, mycobacteria, including *M. leprae*, *M. tuberculosis* and/or *M. avium*, plasmodium, human immunodeficiency virus, Epstein Barr virus, Herpes simplex virus, or hepatitis C virus.

38. The method of claim 28, wherein the GCN2-mediated disorder, disease, or condition is a cancer and the method further comprises administering a second agent for the treatment of cancer.