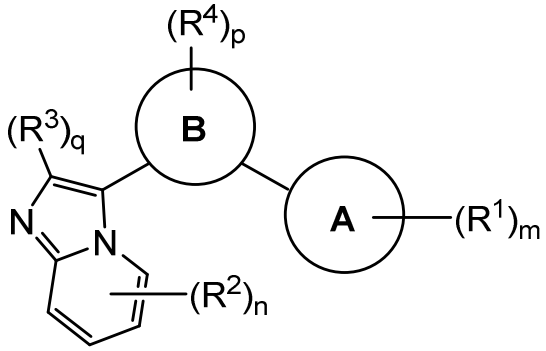
CLAIMS

1. A compound of formula **I**:

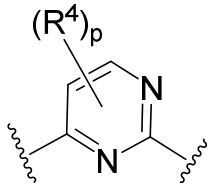
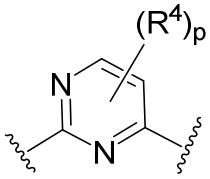
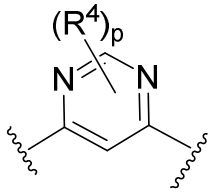


I

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;

Ring B is , , ,

each of R^1 is independently hydrogen, halogen, –CN, $–NO_2$, –C(O)R, –C(O)OR, $–C(O)NR_2$, $–C(O)NRS(O)_2R$, $–C(O)N=S(O)R_2$, $–NR_2$, –NRC(O)R, $–NRC(O)NR_2$, –NRC(O)OR, $–NRS(O)_2R$, $–NRS(O)_2NR_2$, –OR, $–ON(R)SO_2R$, $–P(O)R_2$, –SR, –S(O)R, $–S(O)_2R$, $–S(O)(NH)R$, $–S(O)_2N(R)_2$, $–S(NH_2)_2(O)OH$, $–N=S(O)R_2$, $-CH_3$, $-CH_2OH$, $-CH_2NHSO_2CH_3$, $–CD_3$, $–CD_2NRS(O)_2R$, or R; or:

two R^1 groups are optionally taken together to form =O or =NH; or

two R^1 groups are optionally taken together to form a bivalent C_{2-4} alkylene chain;

each of R^2 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 C_{1-3} 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;

R^3 is hydrogen, halogen, –CN, –OR', $–N(R')_2$, or an optionally substituted group selected from C_{1-3} aliphatic, phenyl, or a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen, halogen, –CN, –OR, $–N=S(O)R_2$, $–N(R)_2$, 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;

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

n is 0, 1, or 2;

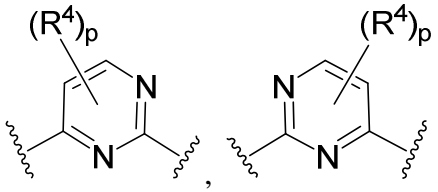
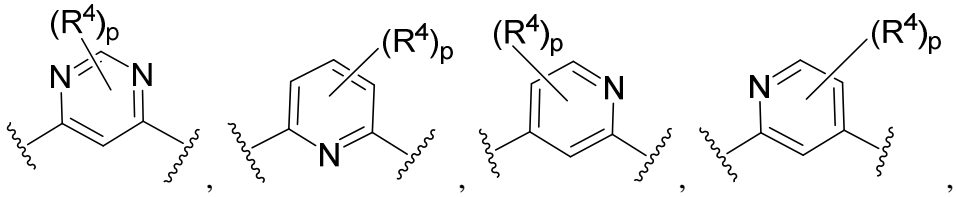
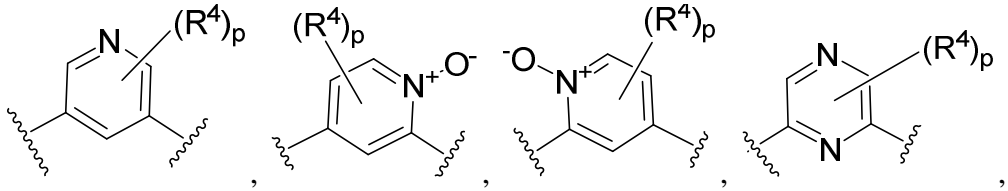
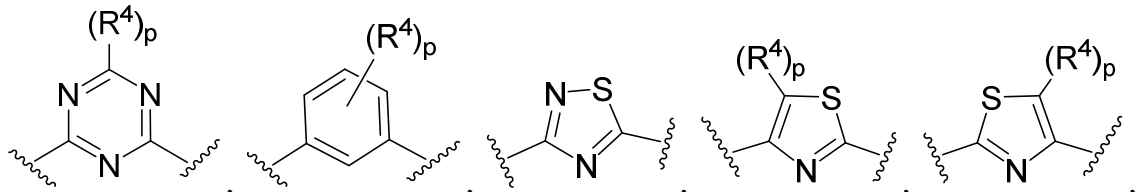
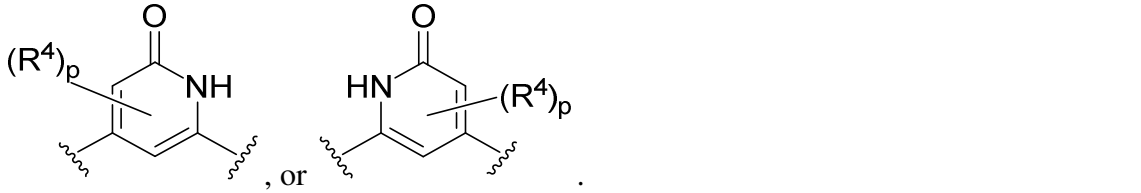
p is 0 or 1; and

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.

4. The compound of claim 1, wherein Ring B is , , , , , or .

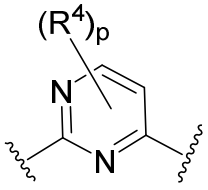
5. The compound of claim 1, wherein each of R^1 is independently hydrogen, halogen, –CN, –C(O)R, –C(O)OR, –C(O)NR_2, –C(O)NRS(O)$_2$R, –C(O)N=S(O)R_2, –NR_2, –NRC(O)R, –NRC(O)NR_2, –NRC(O)OR, –NRS(O)$_2$R, –NRS(O)$_2$$NR_2$, –OR, –ON(R)$SO_2$R, –P(O)$R_2$, –SR, –S(O)R, –S(O)$_2$R, –S(O)(NH)R, –S(O)$_2$N(R)$_2$, –S(N$H_2$)$_2$(O)OH, –N=S(O)$R_2$, -$CH_3$, -$CH_2$OH, -$CH_2NHSO_2CH_3$, –$CD_3$, –$CD_2$NRS(O)$_2$R, 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}

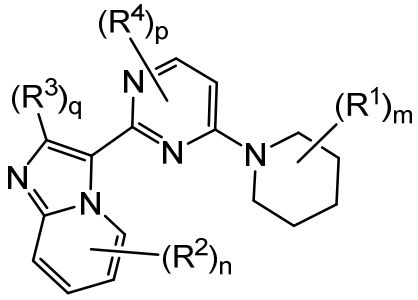
aliphatic, or a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

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.

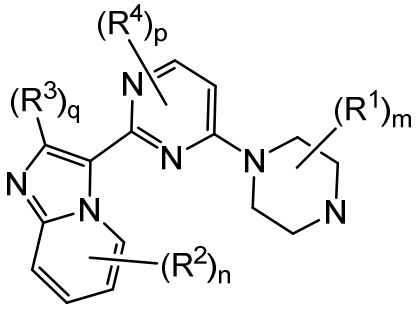
8. The compound of claim 1, wherein R^4 is hydrogen, halogen, –CN, –OR, $–N(R)_2$, or an optionally substituted group selected from C_{1-3} aliphatic, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or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

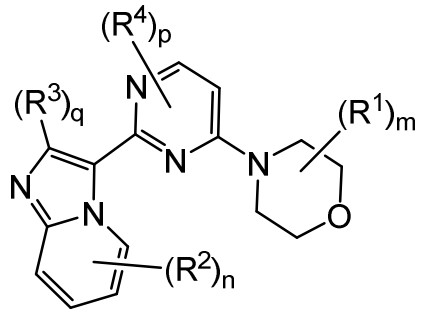
10. The compound of claim 9, of one of formula **IV-a**, **IV-b**, or **IV-c**:



IV-a



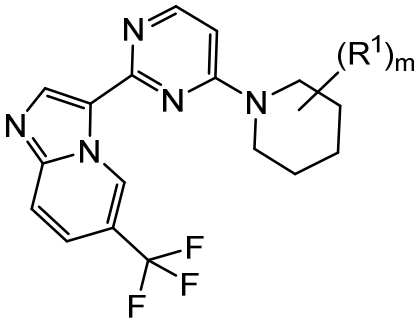
IV-b



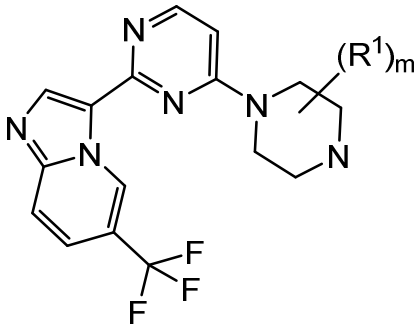
IV-c

or a pharmaceutically acceptable salt thereof.

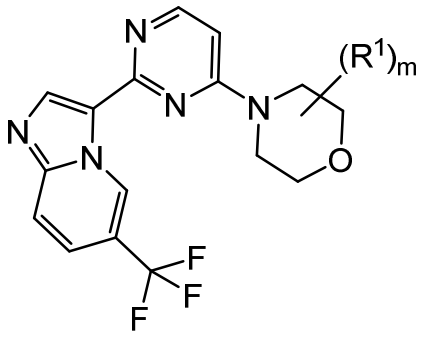
11. The compound of claim 9, of one of formula **XIII-a**, **XIII-a**, or **XIII-c**:



XIII-a



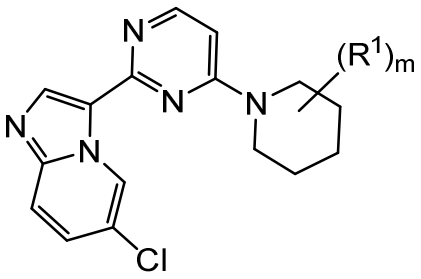
XIII-a



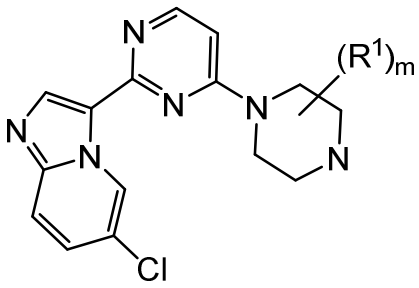
XIII-c

or a pharmaceutically acceptable salt thereof.

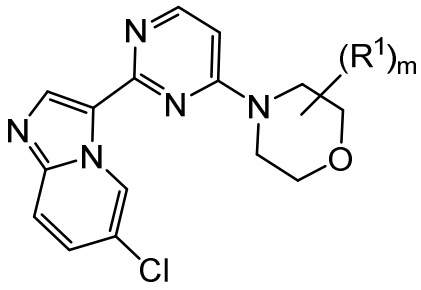
12. The compound of claim 9, of one of formula **XIV-a**, **XIV-a**, or **XIV-c**:



XIV-a



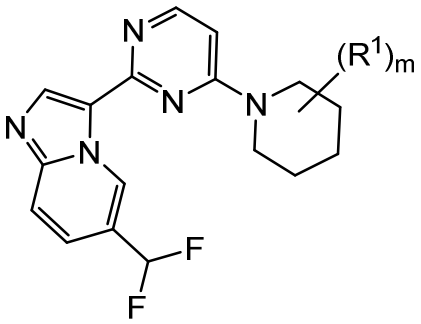
XIV-b



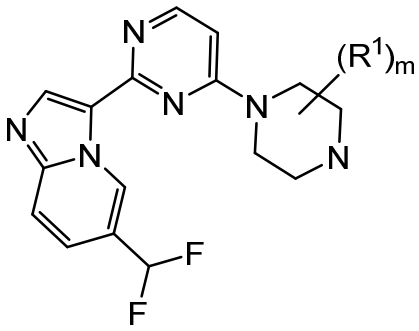
XIV-c

or a pharmaceutically acceptable salt thereof.

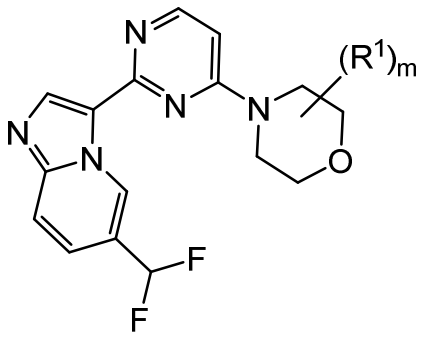
13. The compound of claim 9, of one of formula **XV-a**, **XV-a**, or **XV-c**:



XV-a

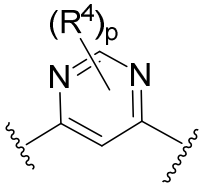


XV-b

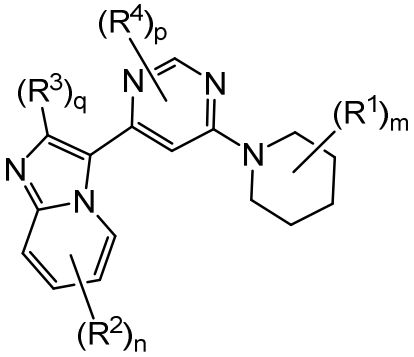


XV-c

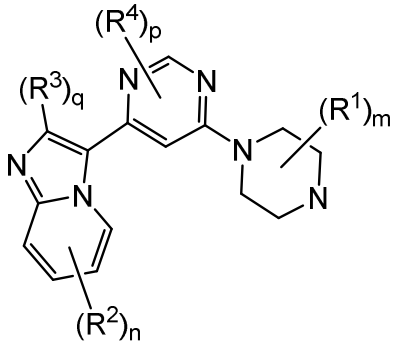
or a pharmaceutically acceptable salt thereof.

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

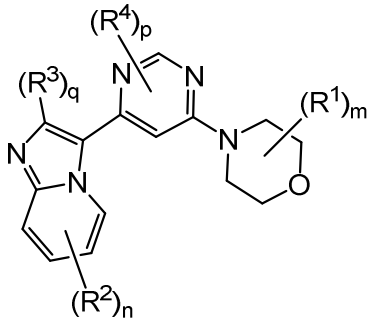
15. The compound of claim 14, of one of formula **VI-a**, **VI-b**, or **VI-c**:



VI-a

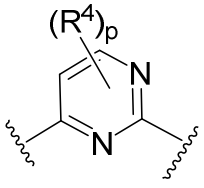


VI-b

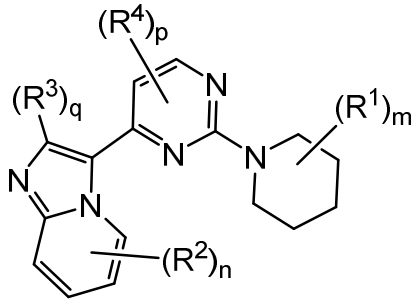


VI-c

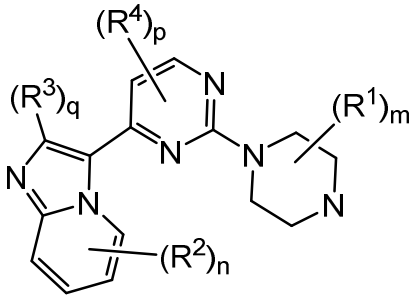
or a pharmaceutically acceptable salt thereof.

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

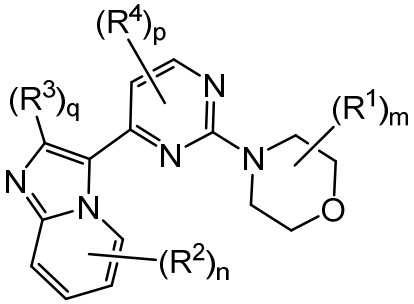
17. The compound of claim 16, of one of formula **XII-a**, **XII-b**, or **XII-c**:



XII-a



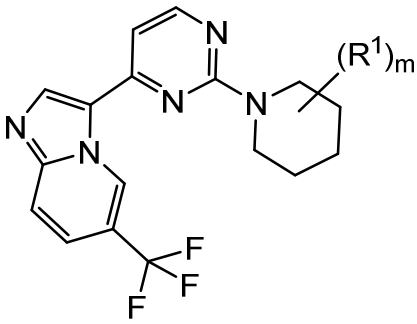
XII-b



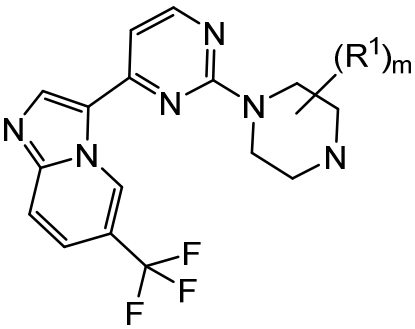
XII-c

or a pharmaceutically acceptable salt thereof.

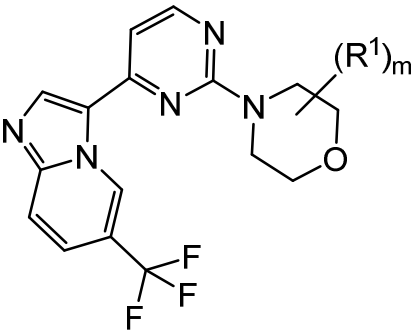
18. The compound of claim 16, of one of formula **XVI-a**, **XVI-b**, or **XVI-c**:



XVI-a



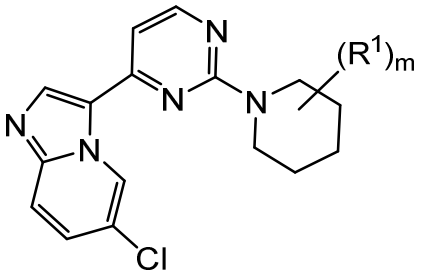
XVI-b



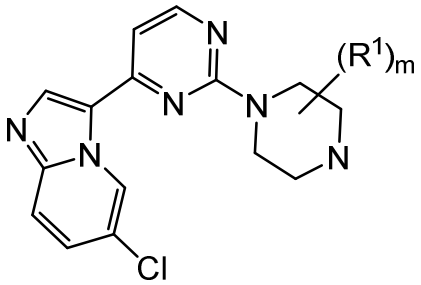
XVI-c

or a pharmaceutically acceptable salt thereof.

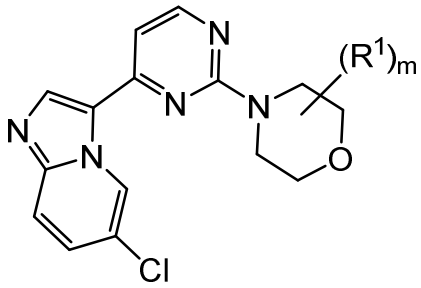
19. The compound of claim 16, of one of formula **XVII-a**, **XVII-b**, or **XVII-c**:



XVII-a



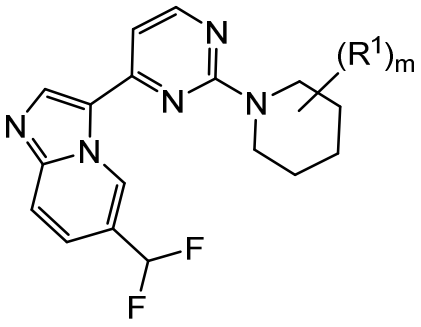
XVII-b



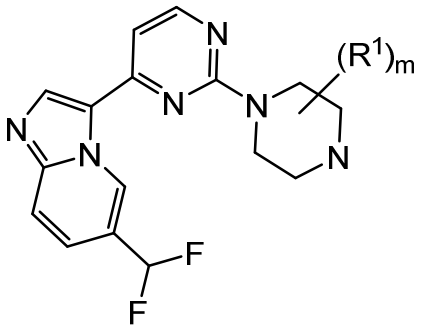
XVII-c

or a pharmaceutically acceptable salt thereof.

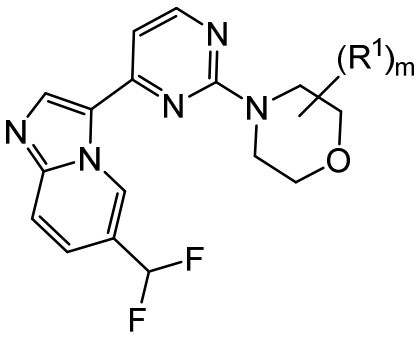
20. The compound of claim 16, of one of formula **XVIII-a**, **XVIII-b**, or **XVIII-c**:



XVIII-a



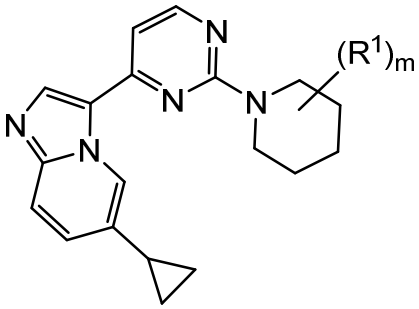
XVIII-b



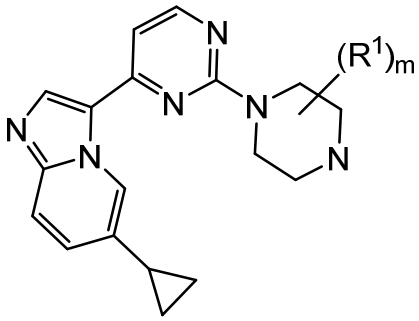
XVIII-c

or a pharmaceutically acceptable salt thereof.

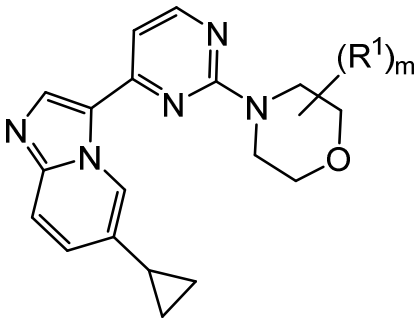
21. The compound of claim 16, of one of formula **XIX-a**, **XIX-b**, or **XIX-c**:



XIX-a



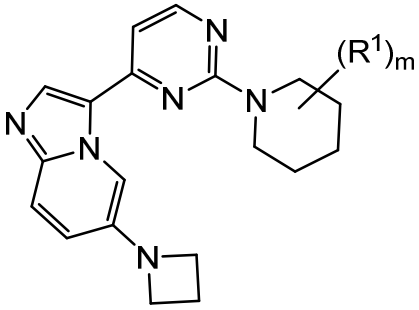
XIX-b



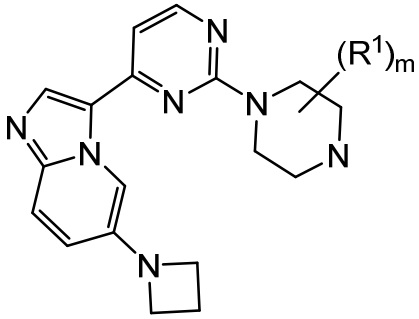
XIX-c

or a pharmaceutically acceptable salt thereof.

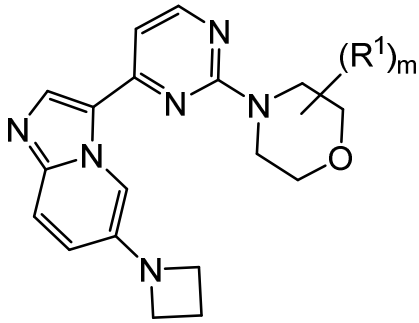
22. The compound of claim 16, of one of formula **XX-a**, **XX-b**, or **XX-c**:



XX-a



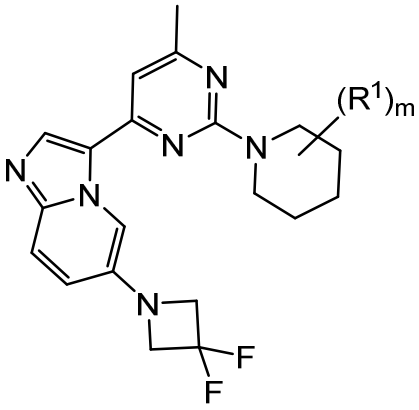
XX-b



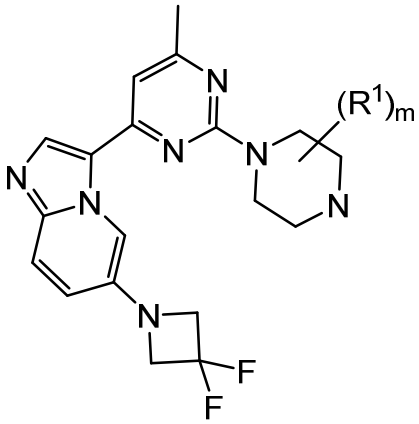
XX-c

or a pharmaceutically acceptable salt thereof.

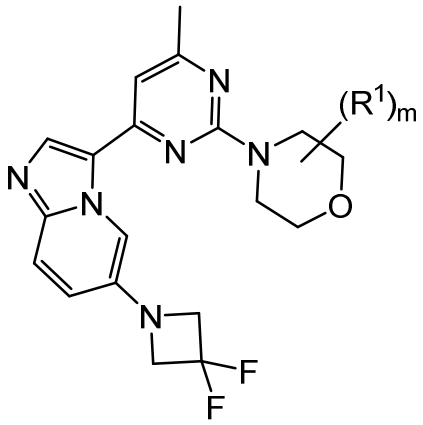
23. The compound of claim 16, of one of formula **XXI-a**, **XXI-b**, or **XXI-c**:



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, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

27. A method of inhibiting GCN2 in a biological sample comprising contacting said biological sample with a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

28. A compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in the inhibition of GCN2 in a patient, or the treatment of a GCN2-mediated disorder, disease, or condition in a patient.

29. Use of the compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment or inhibition of a GCN2-mediated disorder, disease, or condition.

30. The use of claim 29, 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.

31. The use of claim 30, 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.

32. The use of claim 30, wherein the autoimmune condition is rheumatoid arthritis, systemic lupus, multiple sclerosis, psoriasis, Sjögrens syndrome or transplant organ rejection.

33. The use of claim 30, wherein the metabolic condition is diabetes.

34. The use of claim 30, wherein the degenerative disease is osteoarthritis.

35. The use of claim 30, wherein the inflammatory condition is asthma, inflammatory bowel disease, or giant cell arteritis.

36. The use of claim 30, wherein the cardiovascular disease is an ischemic injury.

37. The use of claim 30, 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.

38. The use of claim 30, 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.

39. The use of claim 29, wherein the GCN2-mediated disorder, disease, or condition is a cancer and wherein a second agent is to be administered in conjunction with the medicament for the treatment of cancer.