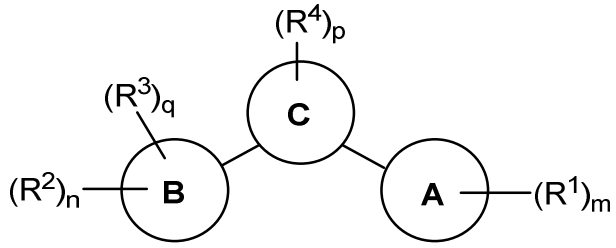
## CLAIMS

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

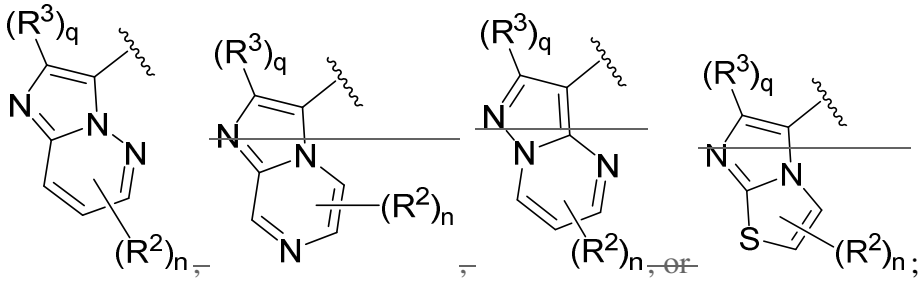


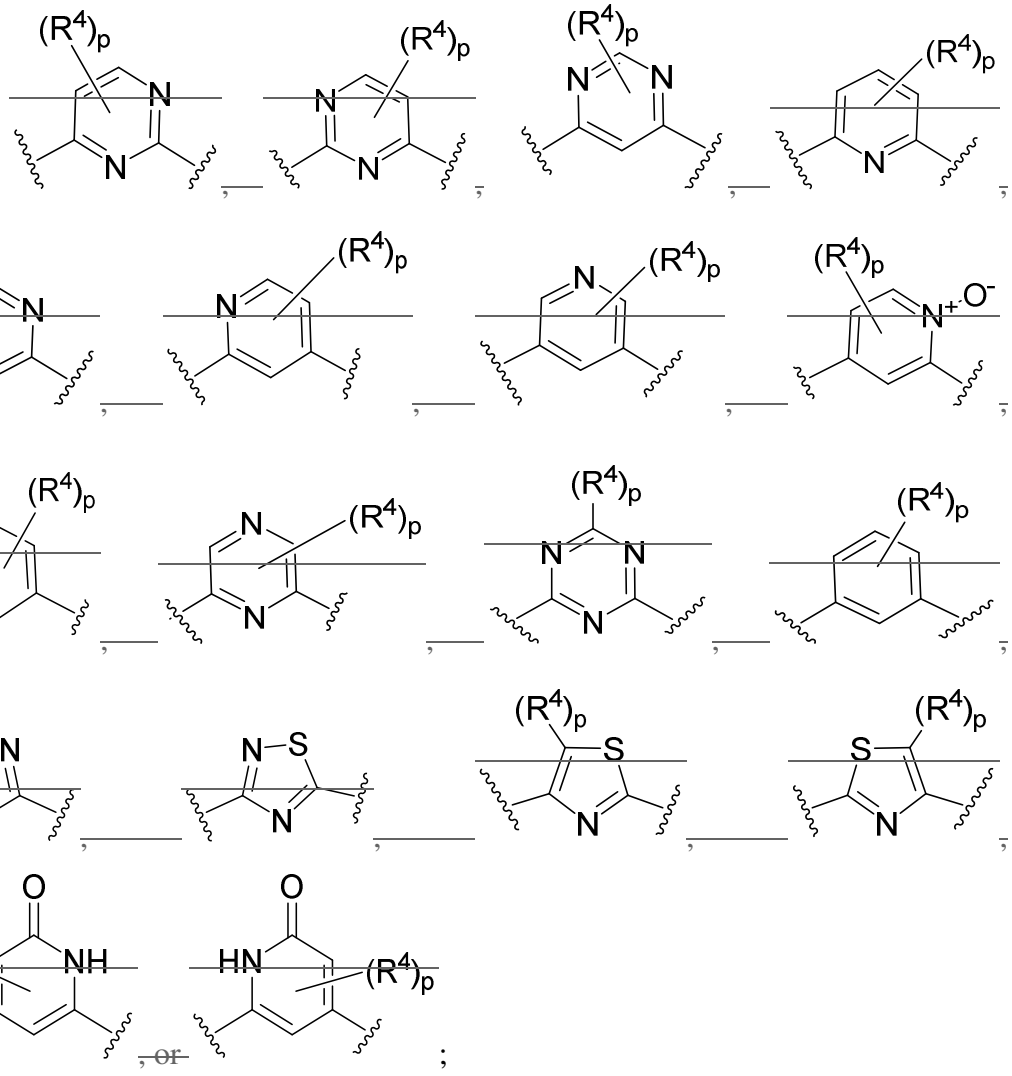

**I**

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 bicyclic heteroaromatic 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 ;

Ring C is ;

each R is independently hydrogen or an optionally substituted group selected from $C_{1-6}$ 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 $C_{2-4}$ 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 $C_{1-3}$ aliphatic group optionally substituted with halogen;

each of $R^1$ is independently hydrogen, halogen, –CN, $–NO_2$, –C(O)R, –C(O)OR, $–C(O)N(R)_2$, $–C(O)N(R)S(O)_2R$, $–C(O)N{=}S(O)(R)_2$, $–N(R)_2$, –N(R)C(O)R, $–N(R)C(O)N(R)_2$, –N(R)C(O)OR, $–N(R)S(O)_2R$, $–N(R)S(O)_2N(R)_2$, –OR, $–ON(R)SO_2R$, $–P(O)(R)_2$, –SR, –S(O)R, $–S(O)_2R$, –S(O)(NH)R, $–S(O)_2N(R)_2$, $–S(NH_2)_2(O)OH$, $–N{=}S(O)(R)_2$, $–C(R)_2S(=O)(=NH)R$, $–C(R)_2NHSO_2CH_3$, $–CD_3$, $–CD_2N(R)S(O)_2R$, or R; or:

two $R^1$ groups are optionally taken together to form =O, =NH or $=NS(O)_2R$; 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;

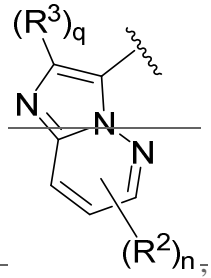
n is 0, 1, or 2;

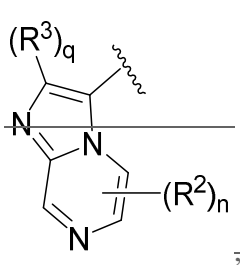
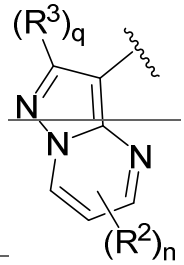
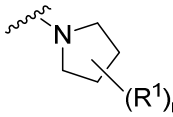
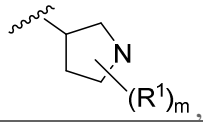
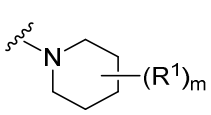
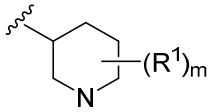
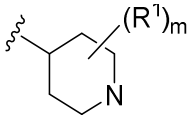
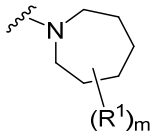
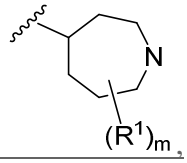
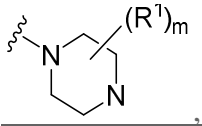
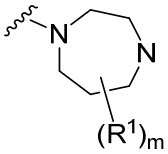
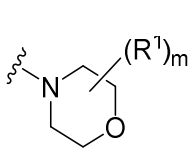
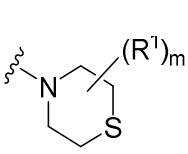
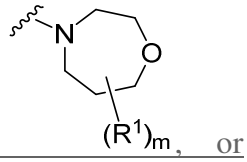
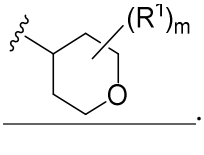
p is 0 or 1; and

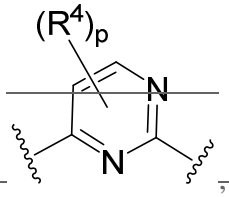
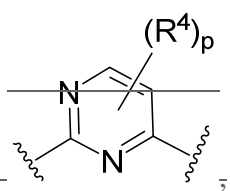
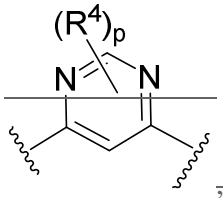
q is 0 or 1.

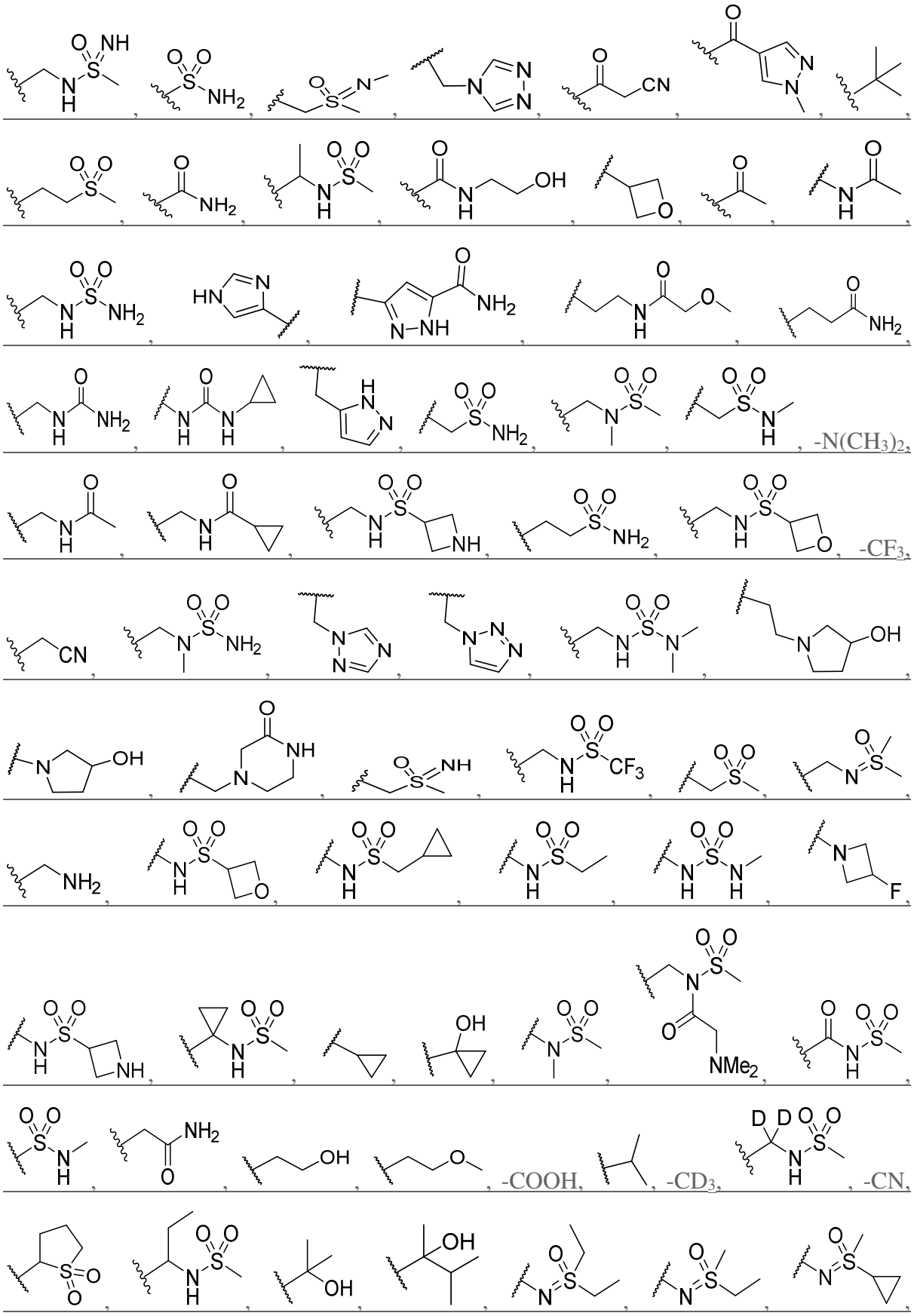
2. The compound of claim 1, wherein Ring A is Het.

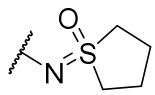
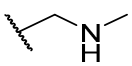
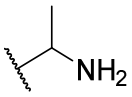
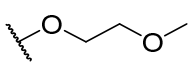
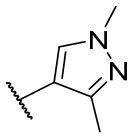
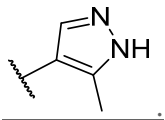
3. The compound of claim 1, wherein Ring A is a 5-7 membered saturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.



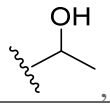
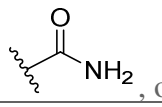
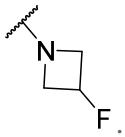
~~34~~. The compound of claim 1, wherein ~~Ring B is~~ , ~~, or~~   Ring A is                  .

4. The compound of claim 1, wherein Ring C is , , ,


-N(CH3)2,
-CF3,
-COOH,
-CD3,
-CN,

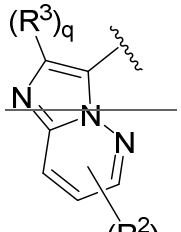
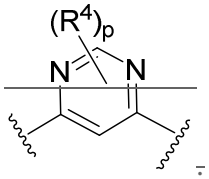
, , , , -$CHF_2$, -$PO(CH_3)_2$, , or .

67. 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.

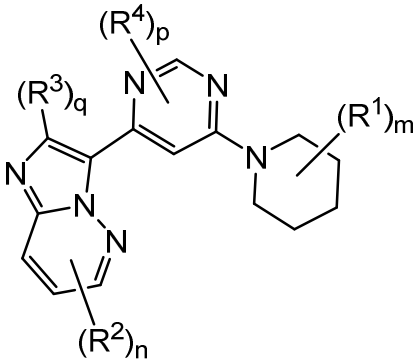
8. The compound of claim 1, wherein each of $R^2$ is independently –Cl, –$CHF_2$, -$CH_2CH_3$, , -$CF_3$, -$CF_2CH_3$, -$CH_3$, , -CN, , or .

79. 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.

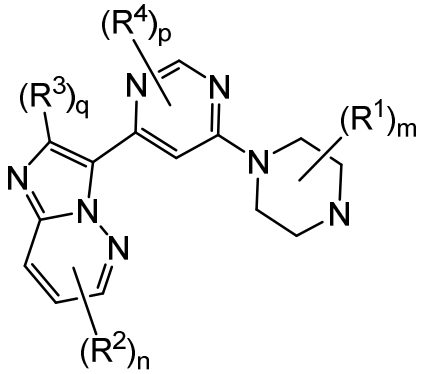
810. The compound of claim 1, wherein $R^4$ is hydrogen, halogen, –CN, –OR, –N(R)$_2$, or an optionally substituted group selected from $C_{1-3}$ aliphatic, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen,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

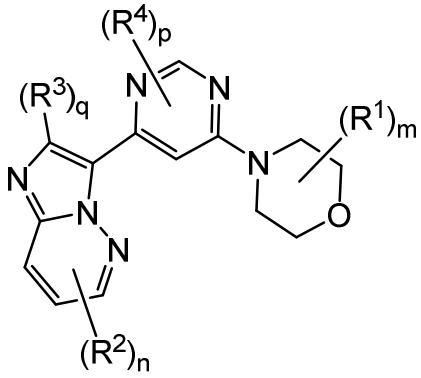
~~10~~11. The compound of any one of claims 1-10~~claim 9~~, of one of formula **X-a**, **X-b**, or **X-c**:



**X-a**

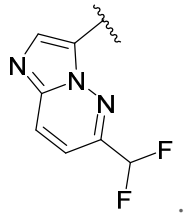


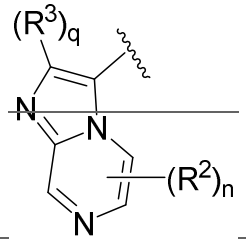
**X-b**

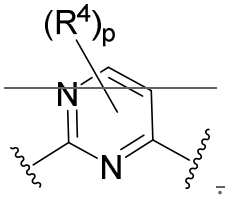


**X-c**

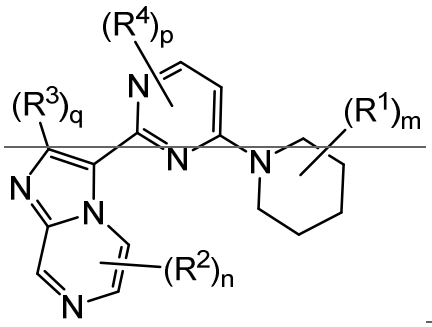
or a pharmaceutically acceptable salt thereof.

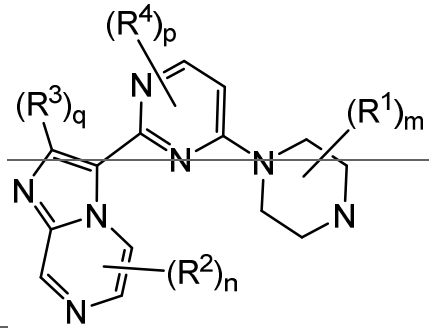
12. The compound of any one of claims 1-11, wherein Ring B is  .

~~11. The compound of claim 1, wherein Ring B is~~  ~~and Ring C is~~

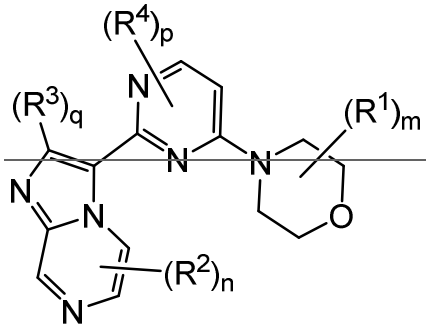


~~12. The compound of claim 11, of one of formula **XVII-a**, **XVII-b**, or **XVII-c**:~~





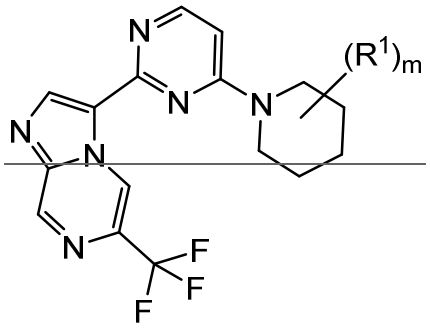
~~**XVII-a** **XVII-b**~~



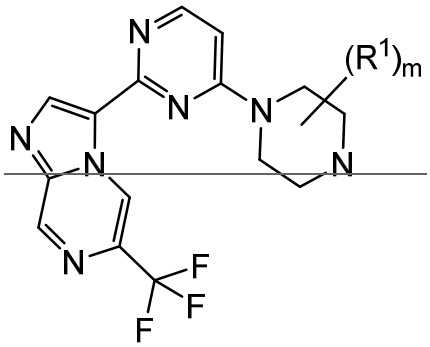
~~**XVII-c**~~

~~or a pharmaceutically acceptable salt thereof.~~

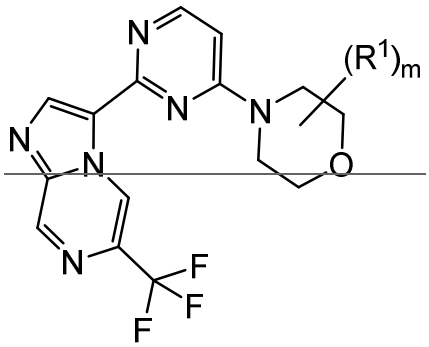
~~13. The compound of claim 11, of one of formula **XXIX-a**, **XXIX-b**, or **XXIX-c**:~~



~~**XXIX-a**~~



~~**XXIX-b**~~

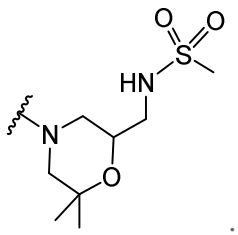


~~**XXIX-c**~~

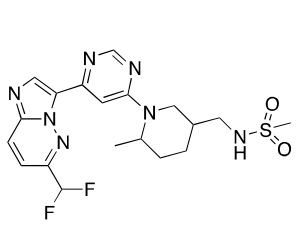
~~or a pharmaceutically acceptable salt thereof.~~

13. The compound of any one of claims 1-12, wherein n is 1.

14. The compound of any one of claims 1 to 13, wherein m is 1, 2, 3, 4 or 5, in particular 1, 2 or 3.

15. The compound of claim 1, wherein Ring A is .

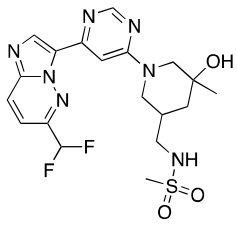
~~15~~16. The compound of claim 1 wherein the compound is selected from ~~those depicted in Tables 1-4~~



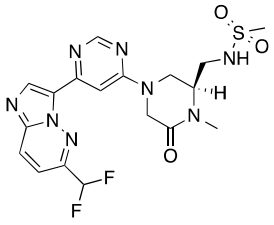
II-3



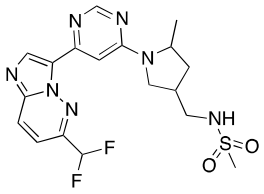
II-4



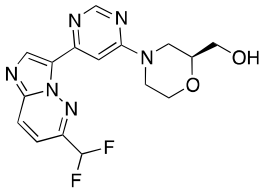
II-5



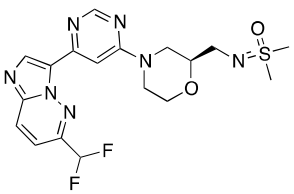
II-7



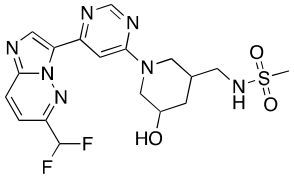
II-8



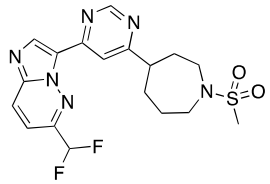
II-9



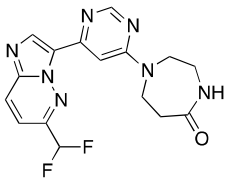
II-10



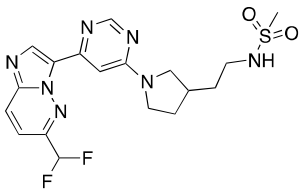
II-12



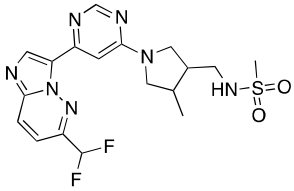
II-14



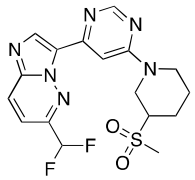
II-15



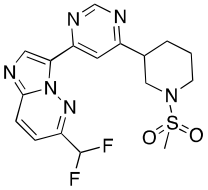
II-17



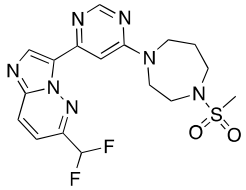
II-18



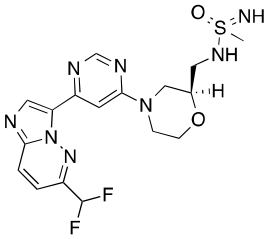
II-19



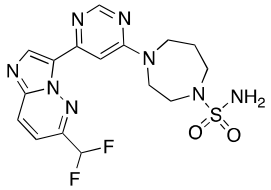
II-21



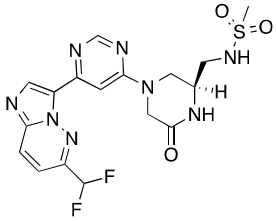
II-22



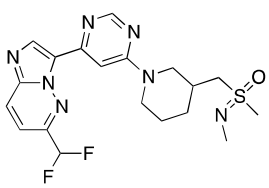
II-23



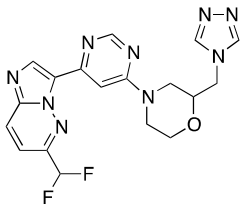
II-24



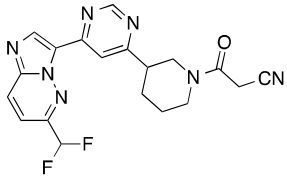
II-25



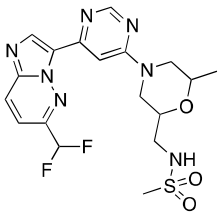
II-26



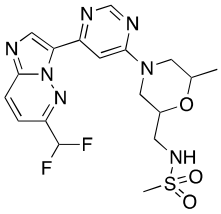
II-29



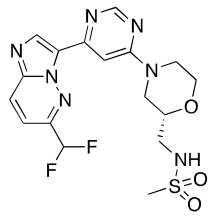
II-30



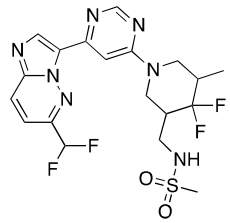
II-31



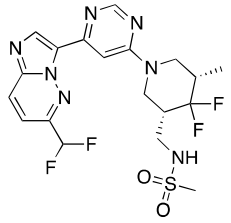
II-33



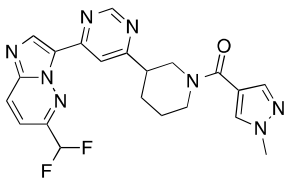
II-34



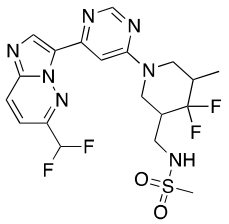
**II-35**



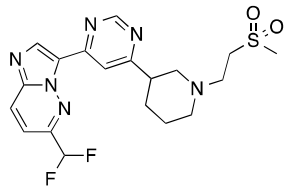
**II-36**



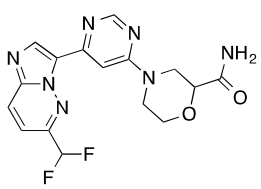
**II-41**



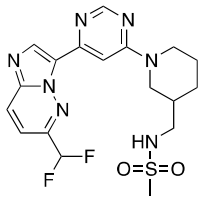
**II-45**



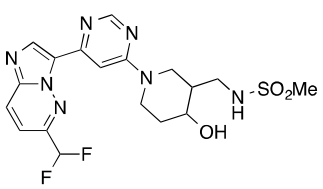
**II-48**



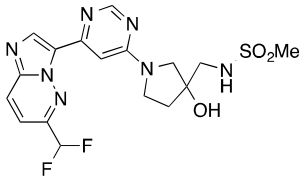
**II-50**



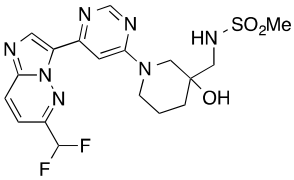
**II-59**



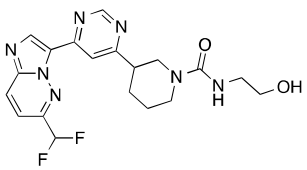
**II-112**



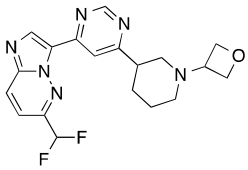
**II-137**



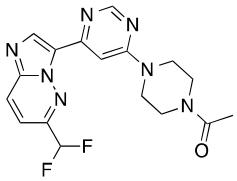
**II-158**



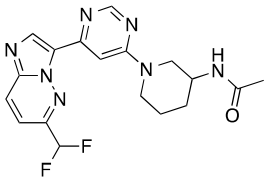
**II-178**



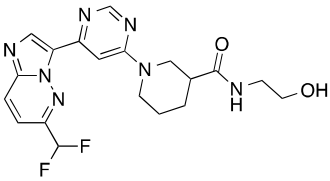
**II-180**



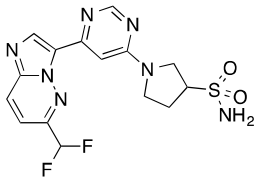
**II-186**



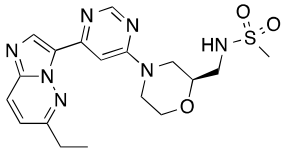
**II-190**



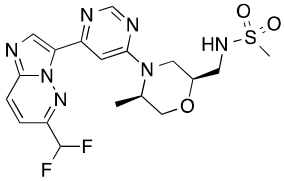
**II-191**



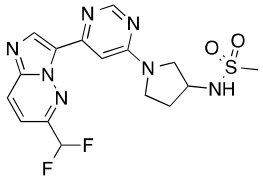
**II-192**



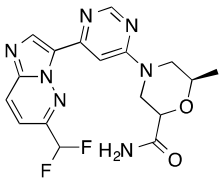
**II-196**



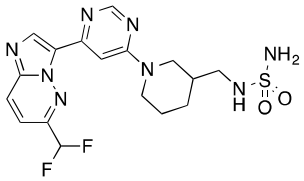
**II-197**



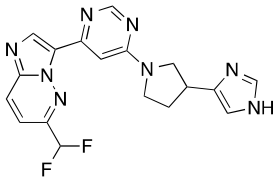
**II-199**



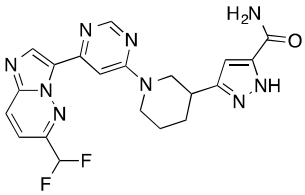
**II-201**



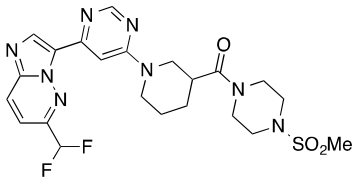
**II-202**



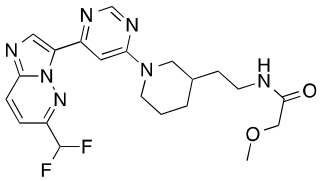
**II-203**



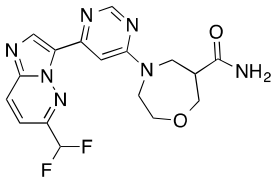
**II-205**



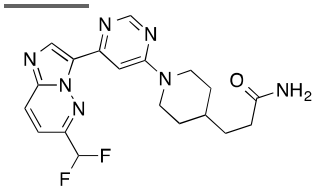
**II-206**



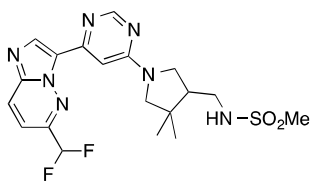
**II-209**



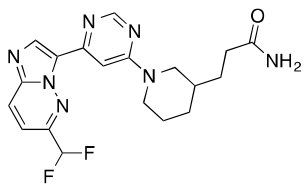
**II-210**



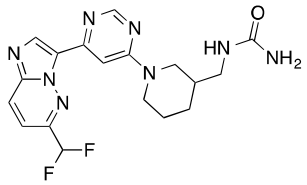
II-212



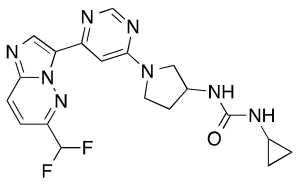
II-213



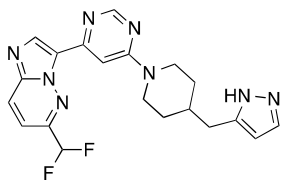
II-214



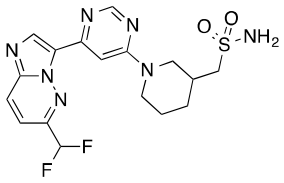
II-215



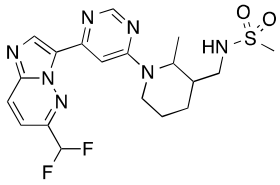
II-216



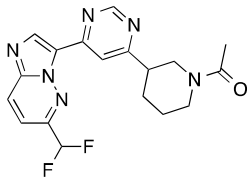
II-217



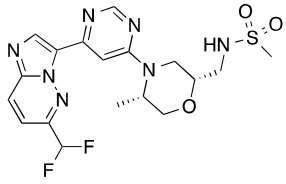
II-219



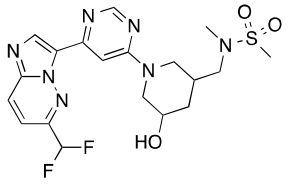
II-221



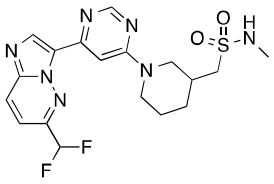
II-222



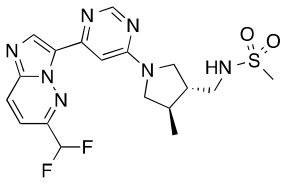
II-234



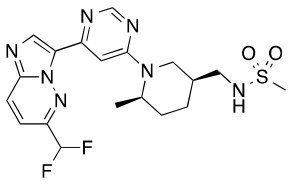
II-235



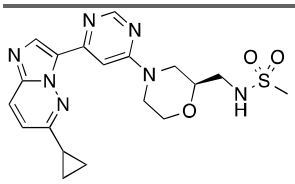
II-236



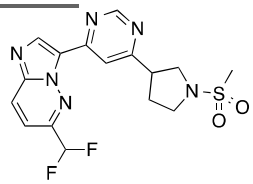
II-237



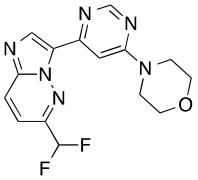
II-247



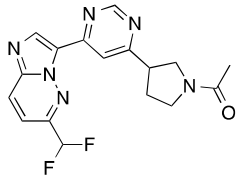
II-249



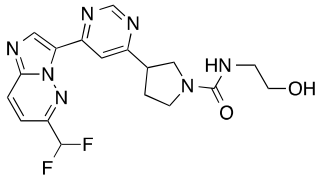
II-250



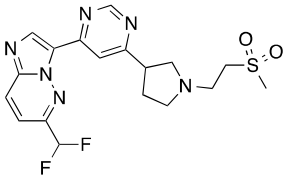
II-251



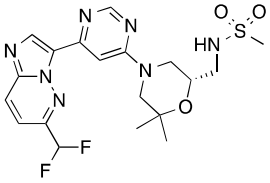
II-253



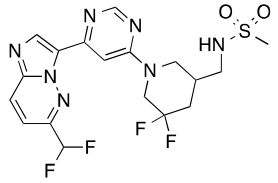
II-254



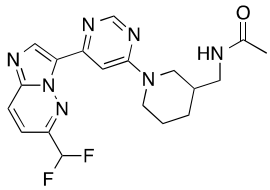
II-255



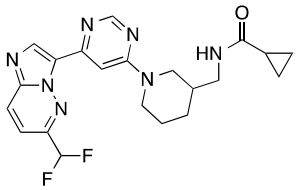
II-257



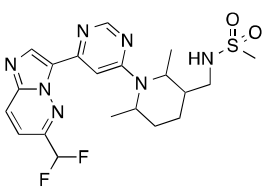
II-258



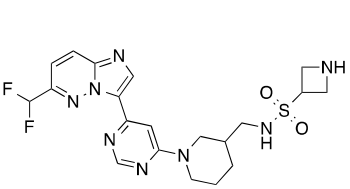
II-261



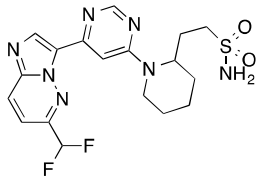
II-262



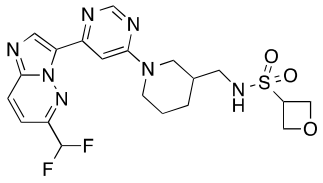
II-268



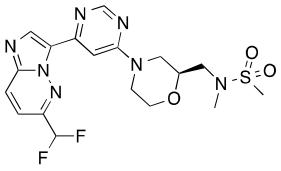
II-272



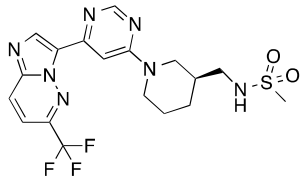
II-283



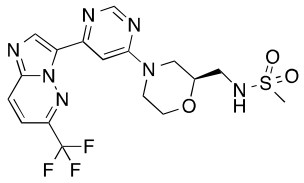
II-289



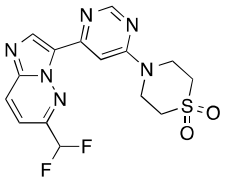
II-290



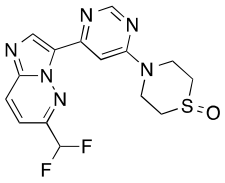
II-291



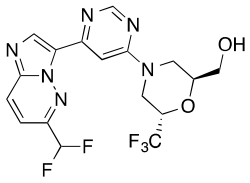
II-292



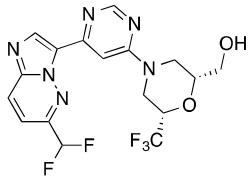
II-295



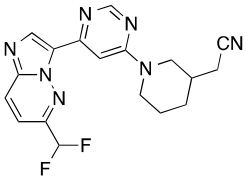
II-296



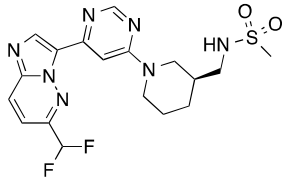
II-297



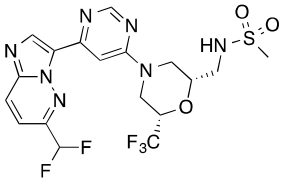
II-298



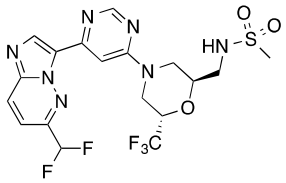
II-299



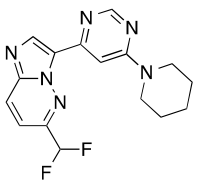
II-300



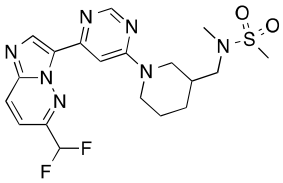
II-306



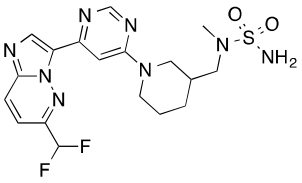
II-307



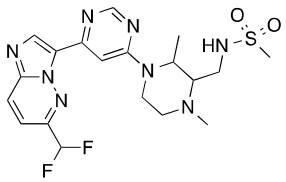
II-308



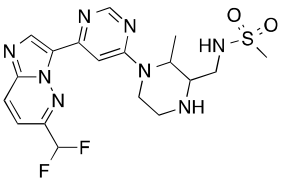
II-310



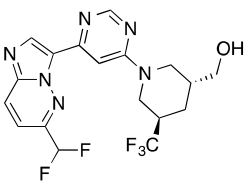
II-311



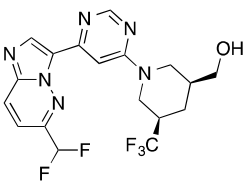
II-312



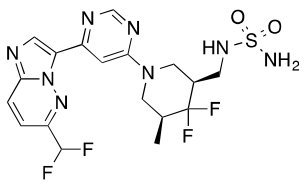
II-313



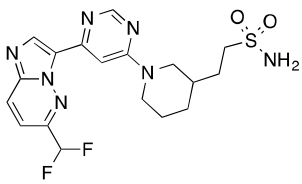
II-314



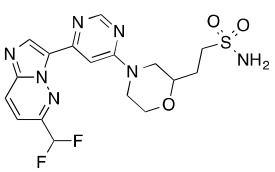
II-315



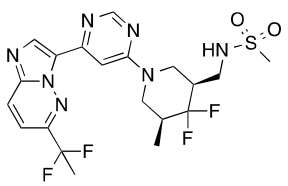
II-316



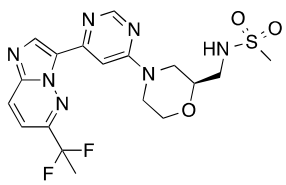
II-317



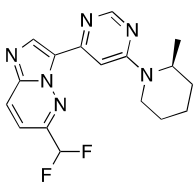
II-318



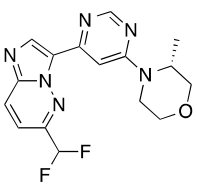
II-321



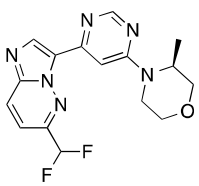
II-322



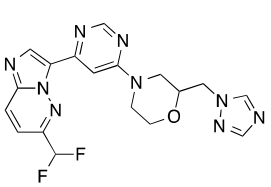
II-323



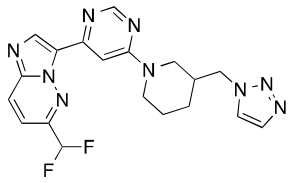
II-324



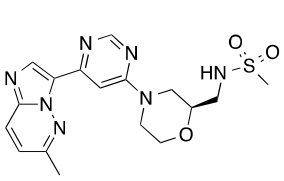
II-325



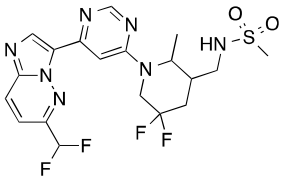
II-326



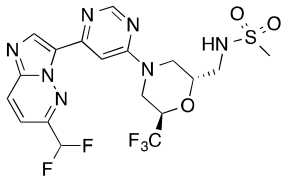
**II-327**



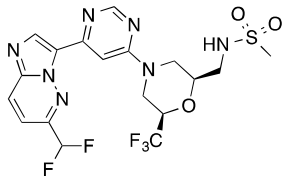
**II-328**



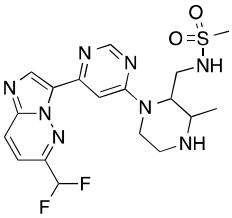
**II-329**



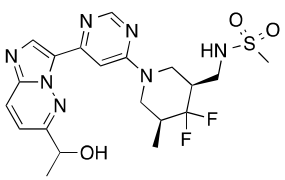
**II-330**



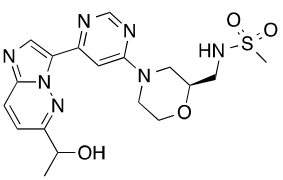
**II-331**



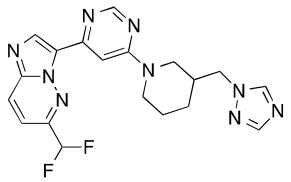
**II-336**



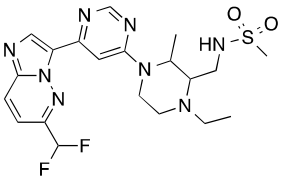
**II-337**



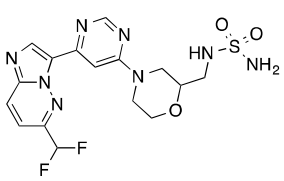
**II-338**



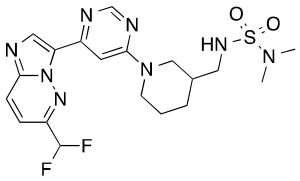
**II-339**



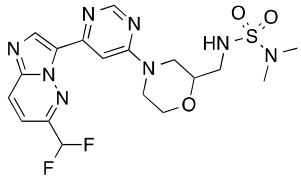
**II-340**



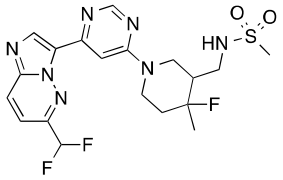
**II-347**



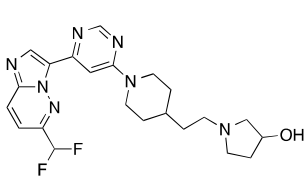
**II-348**



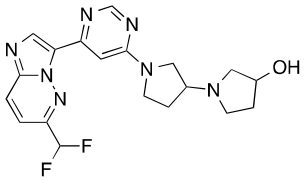
**II-349**



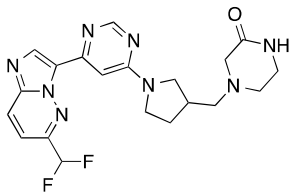
**II-350**



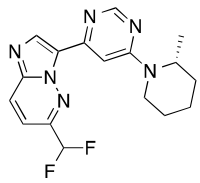
**II-351**



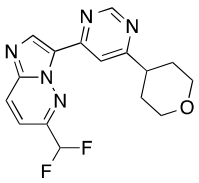
**II-352**



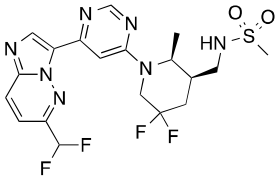
**II-353**



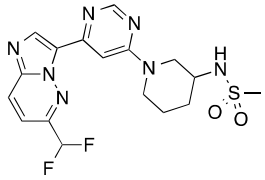
**II-354**



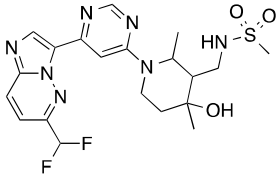
**II-358**



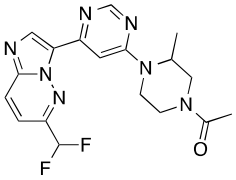
**II-361**



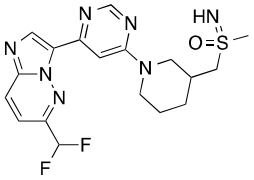
**II-362**



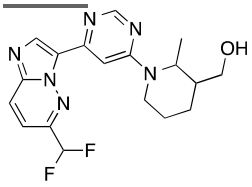
**II-366**



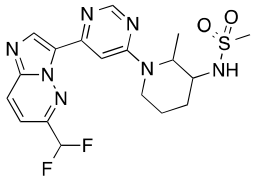
**II-368**



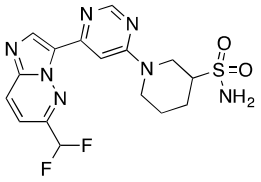
**II-370**



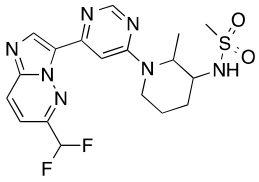
**II-373**



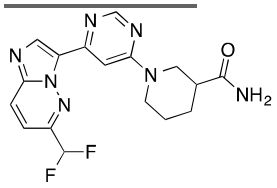
**II-374**



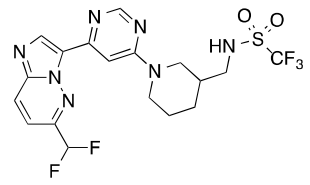
**II-376**



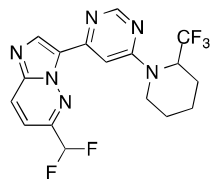
**II-377**



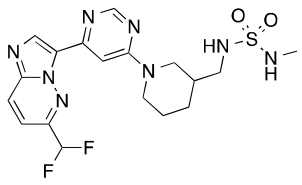
**II-378**



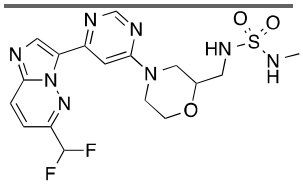
**II-379**



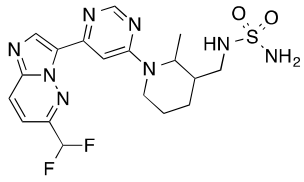
**II-380**



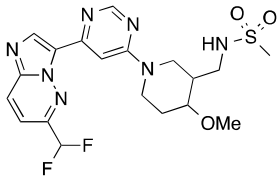
**II-385**



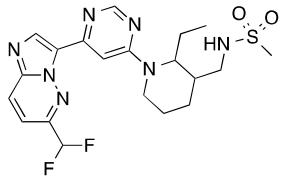
**II-386**



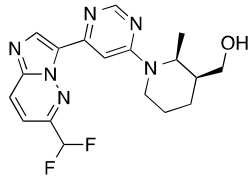
**II-387**



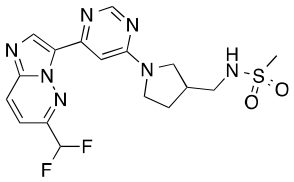
**II-390**



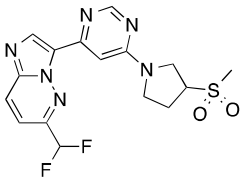
**II-391**



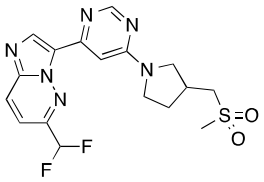
**II-392**



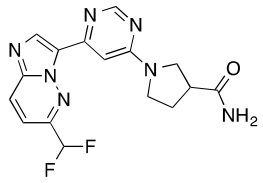
**II-394**



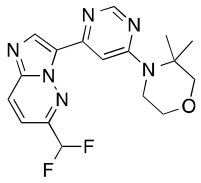
**II-395**



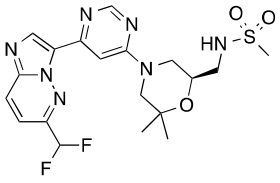
**II-396**



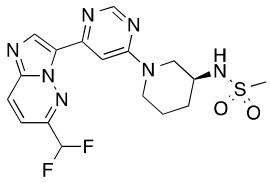
**II-399**



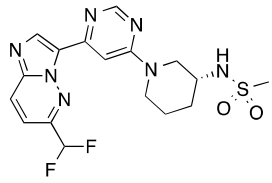
**II-402**



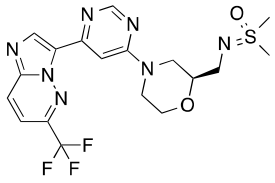
**II-403**



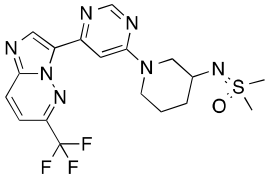
**II-404**



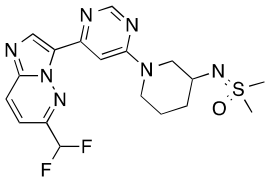
**II-405**



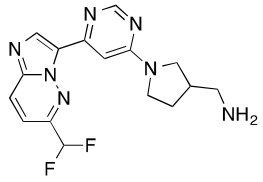
**II-406**



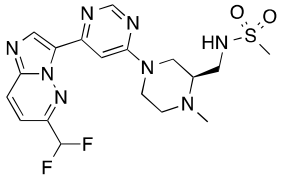
**II-407**



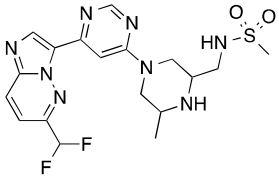
**II-408**



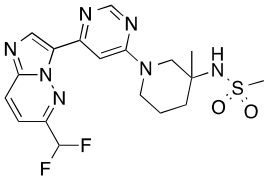
**II-409**



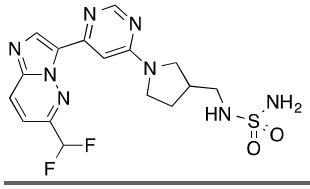
**II-410**



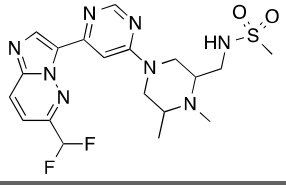
**II-411**



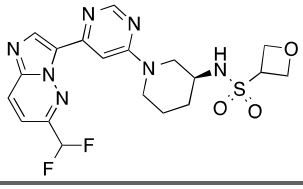
**II-412**



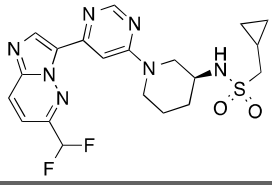
**II-415**



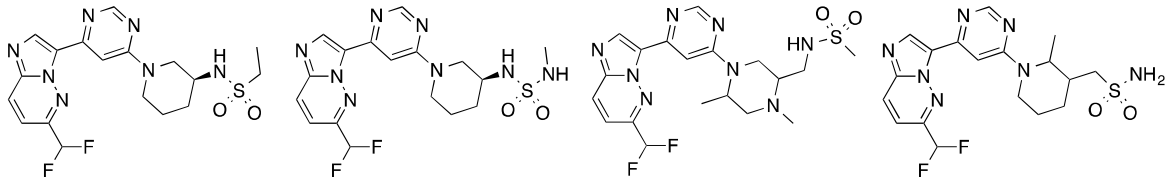
**II-418**



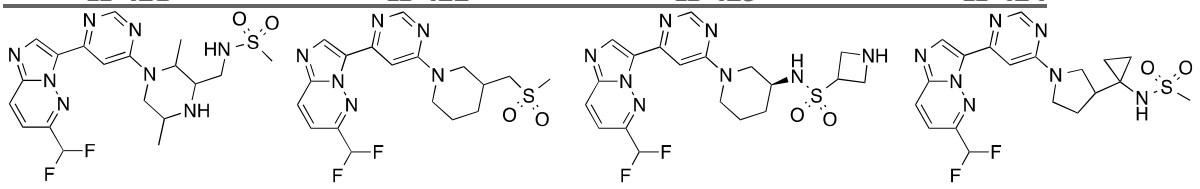
**I-419**



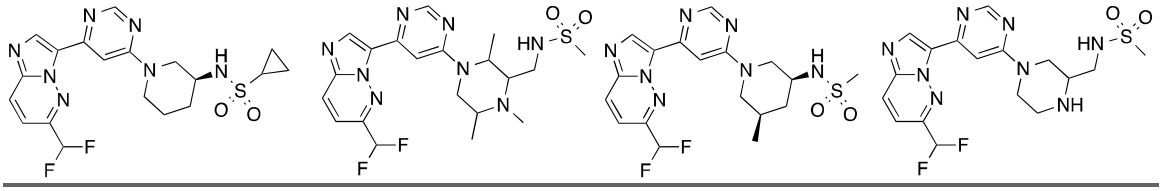
**II-420**



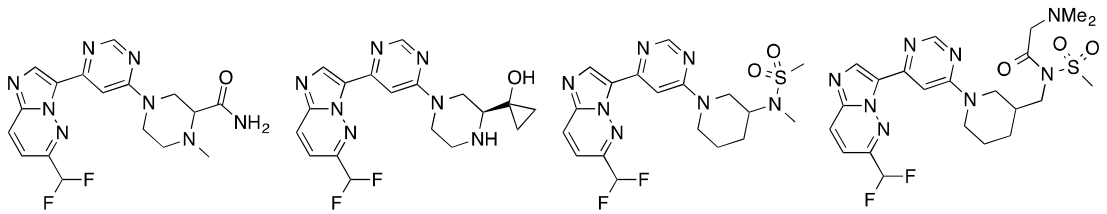
II-421 II-422 II-423 II-424



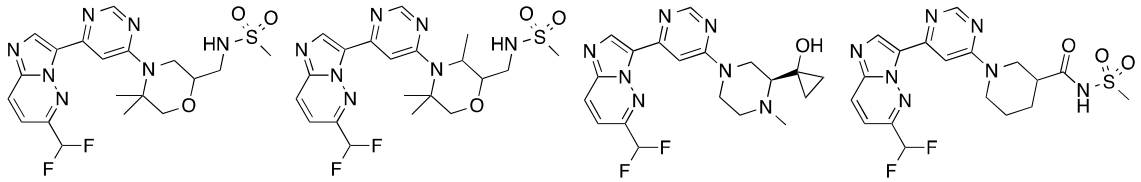
II-427 II-430 II-435 II-439



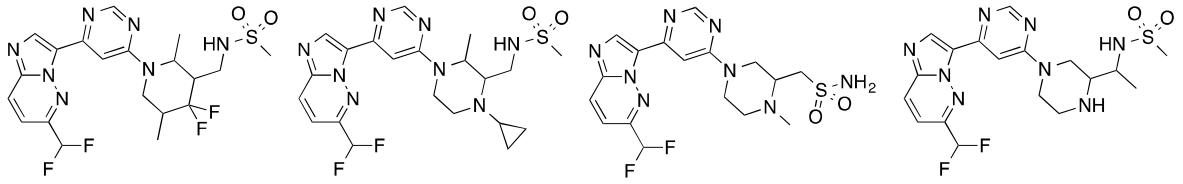
II-442 II-448 II-449 II-450



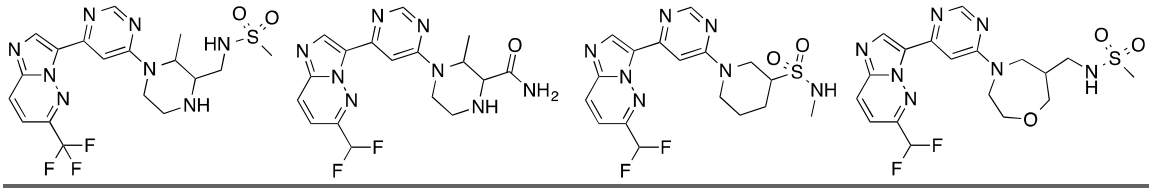
II-453 II-454 II-455 II-456



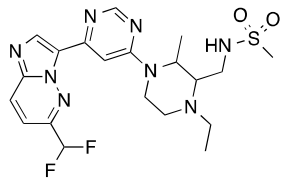
II-457 II-458 II-459 II-460



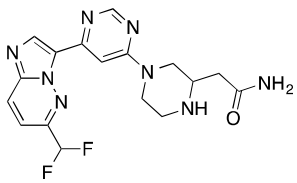
II-462 II-463 II-464 II-465



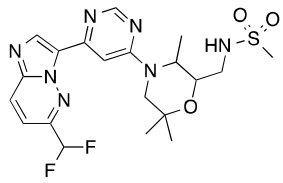
II-466 II-477 II-480 II-481



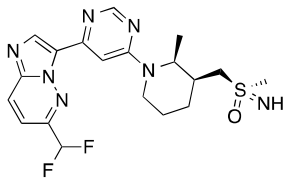
II-482



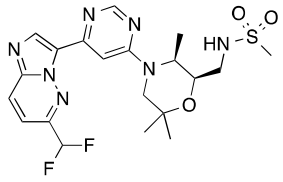
II-483



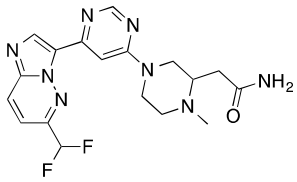
II-484



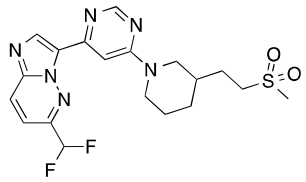
II-485



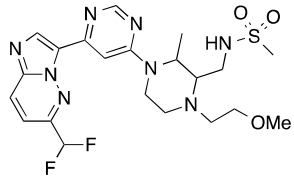
II-490



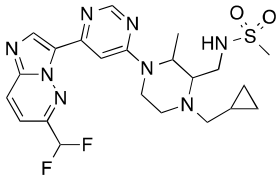
II-492



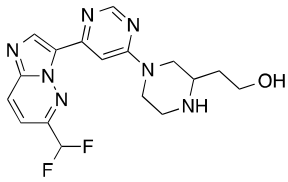
II-493



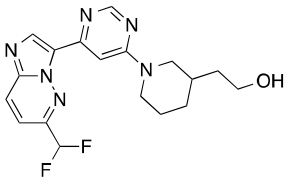
II-494



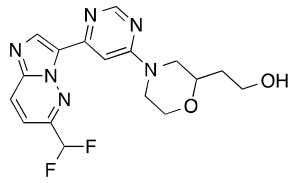
II-495



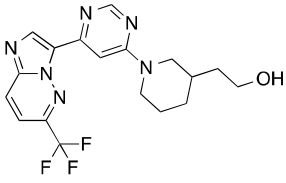
II-496



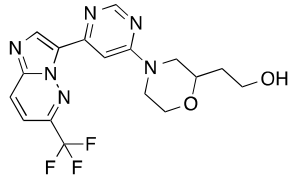
II-497



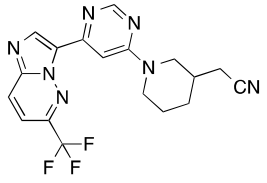
II-498



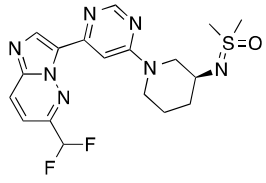
II-499



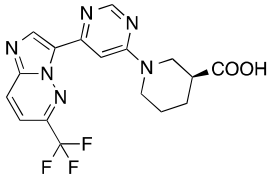
II-500



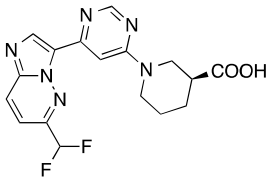
II-501



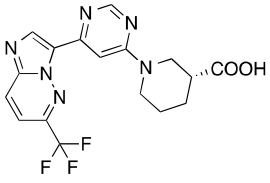
II-502



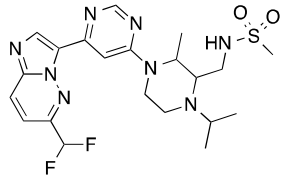
II-504



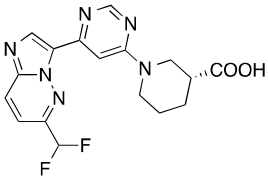
II-505



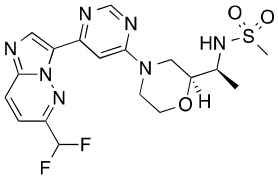
II-506



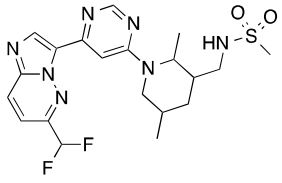
II-507



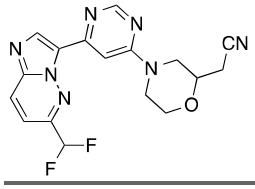
II-508



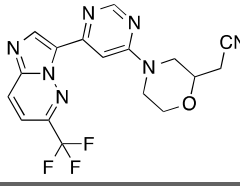
II-509



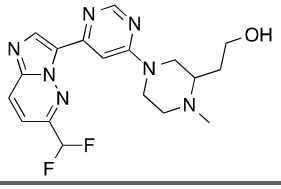
II-511



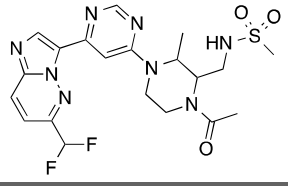
II-512



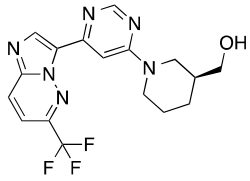
II-513



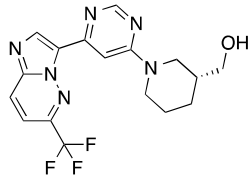
II-514



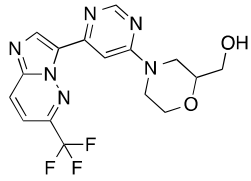
II-515



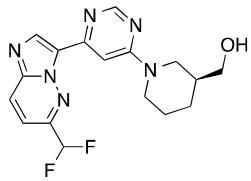
**II-516**



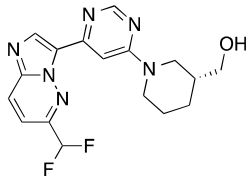
**II-517**



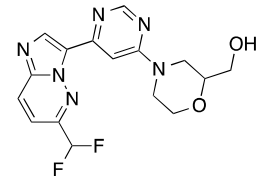
**II-518**



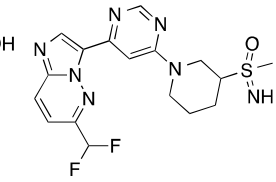
**II-519**



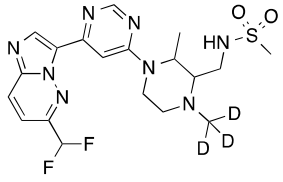
**II-520**



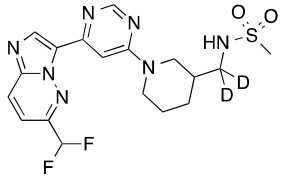
**II-521**



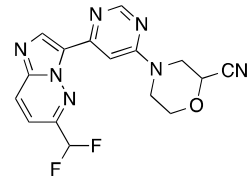
**II-522**



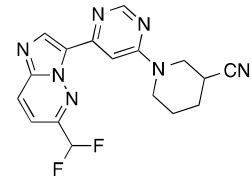
**II-523**



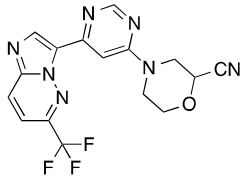
**II-524**



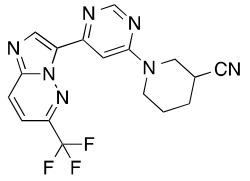
**II-531**



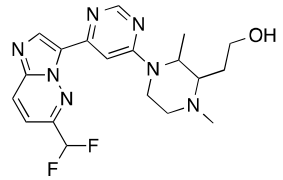
**II-532**



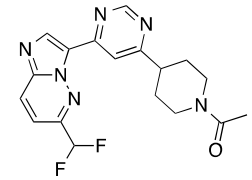
**II-533**



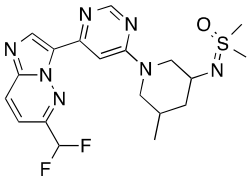
**II-534**



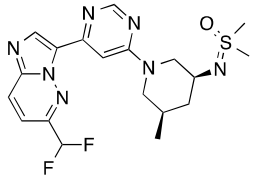
**II-536**



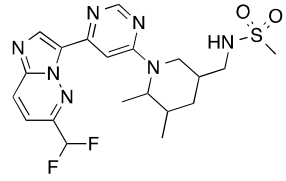
**II-539**



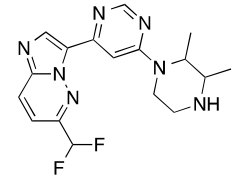
**II-540**



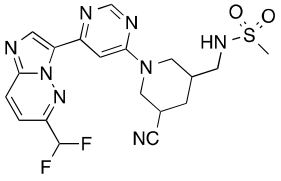
**II-541**



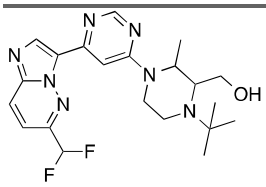
**II-544**



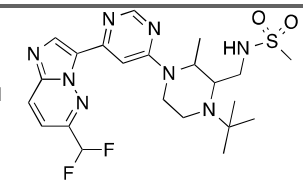
**II-548**



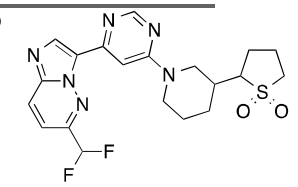
**II-553**



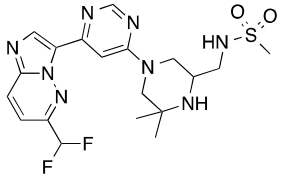
**II-556**



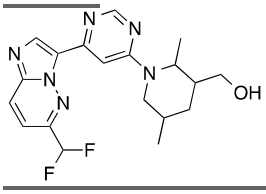
**II-559**



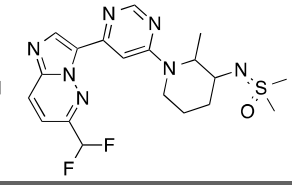
**II-563**



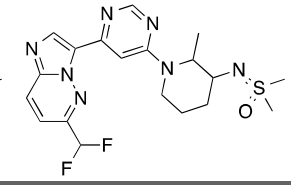
**II-567**



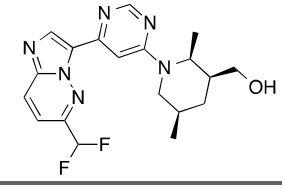
**II-577**



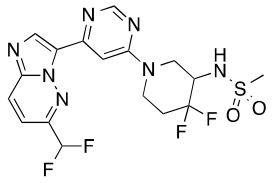
**II-578**



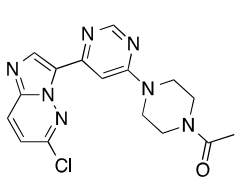
**II-579**



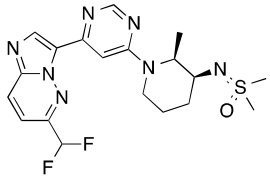
**II-585**



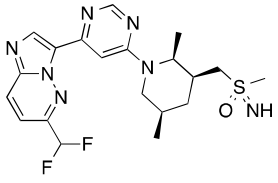
II-589



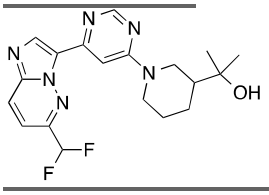
II-590



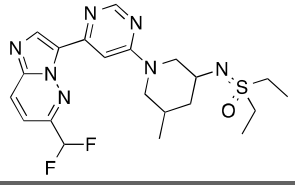
II-593



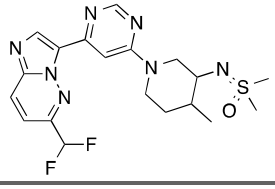
II-607



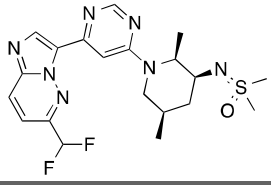
II-608



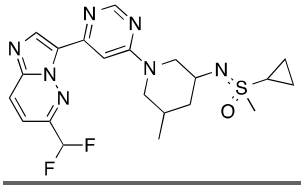
II-627



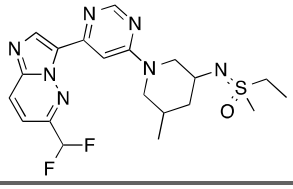
II-629



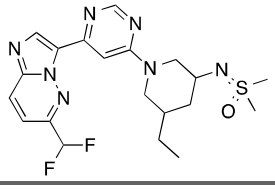
II-631



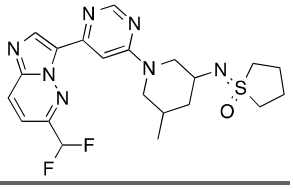
II-634



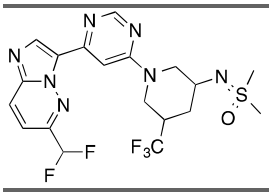
II-635



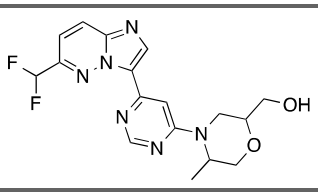
II-648



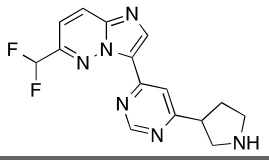
II-649



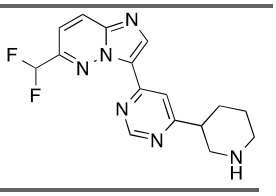
II-654



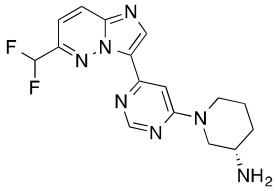
II-657



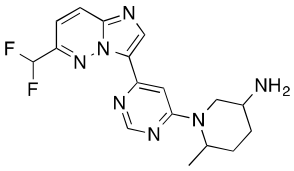
II-658



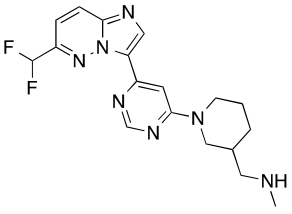
II-659



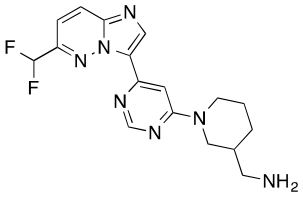
II-661



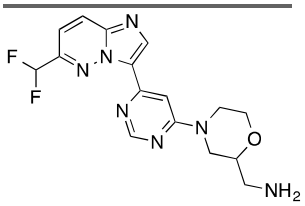
II-663



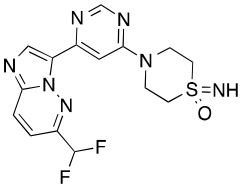
II-666



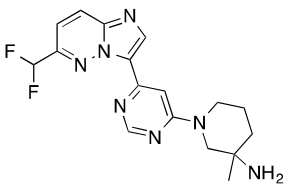
II-671



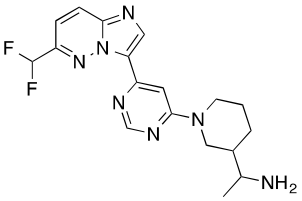
II-672



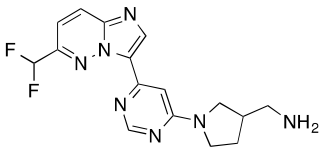
II-676

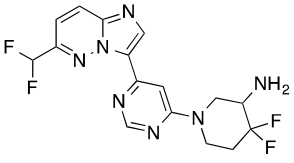


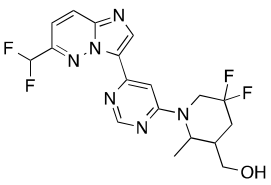
II-678

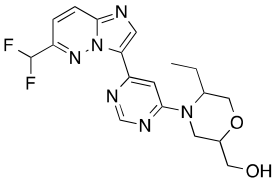


II-680

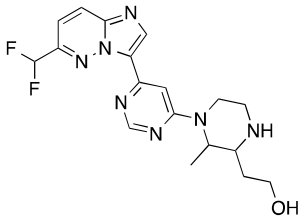




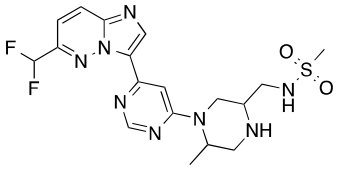




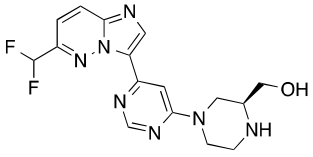
**II-681**



**II-682**

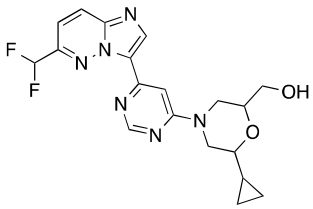


**II-684**

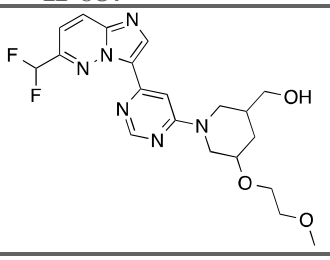


**II-685**

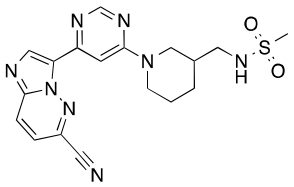
**II-686**



**II-687**



**II-688**



**II-689**



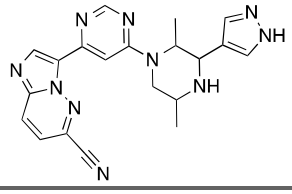
**II-690**



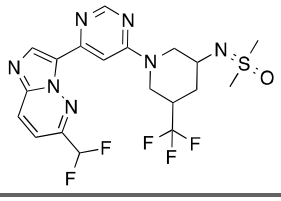
**II-692**



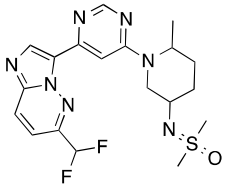
**II-693**



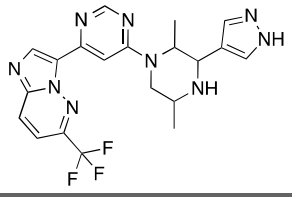
**II-694**



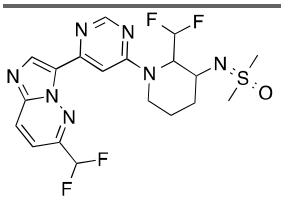
**II-696**



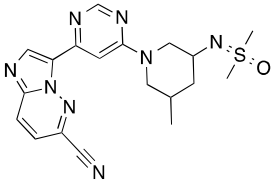
**II-698**



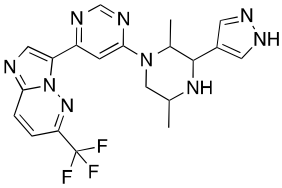
**II-700**



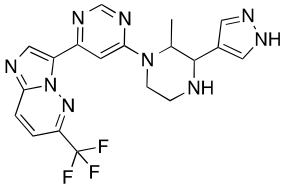
**II-702**



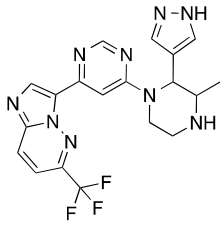
**II-704**



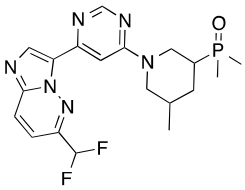
**II-706**



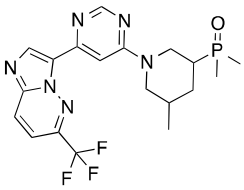
**II-707**



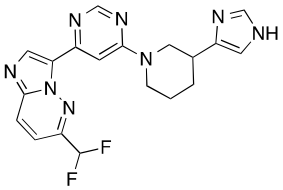
**II-710**



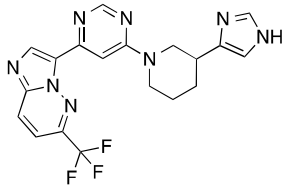
**II-712**



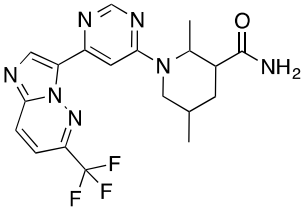
**II-714**



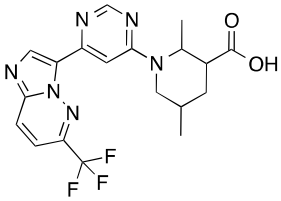
**II-715**

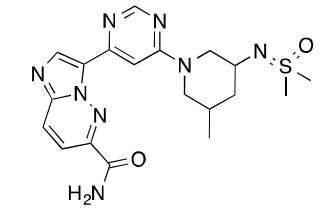


**II-719**

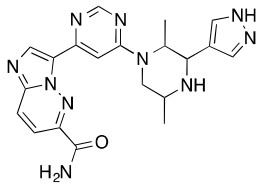


**II-721**

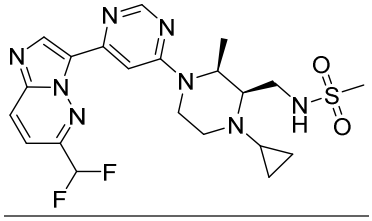




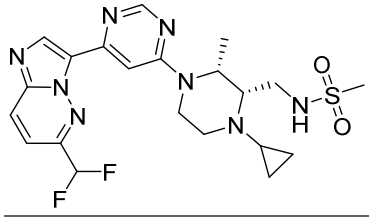
II-726



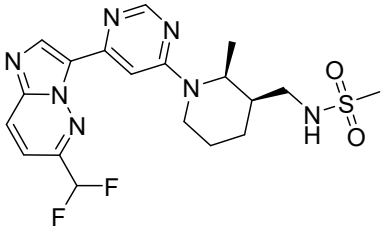
II-728



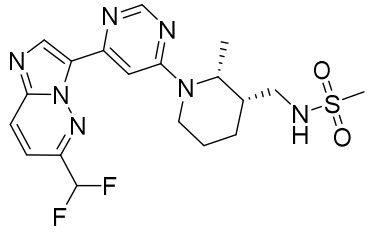
II-752



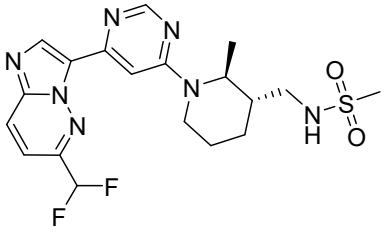
II-753



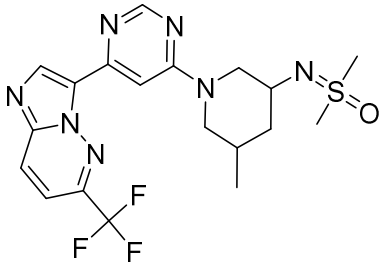
II-754



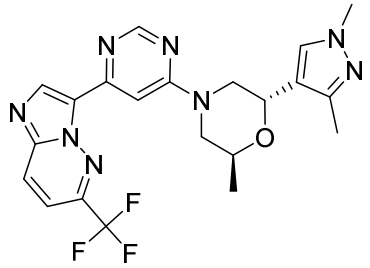
II-755



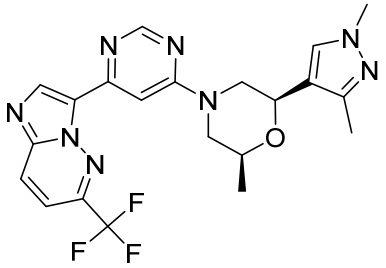
II-756



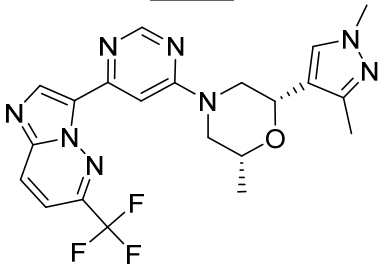
II-757



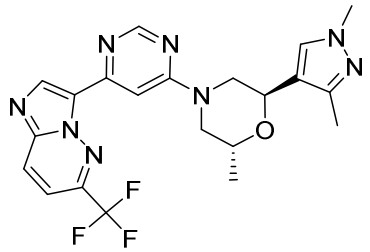
II-758



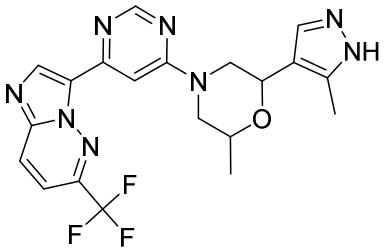
II-759



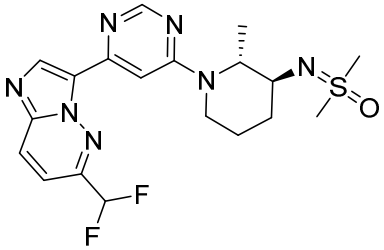
II-760



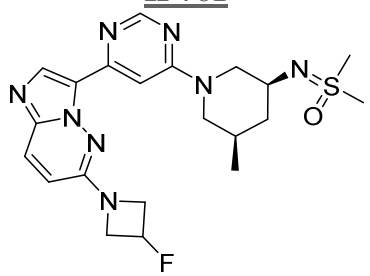
II-761



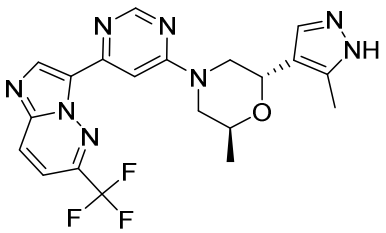
II-762



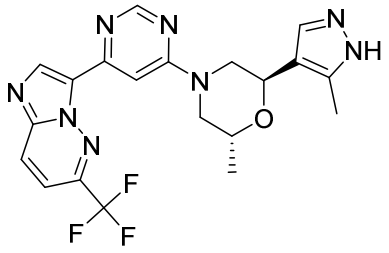
II-763



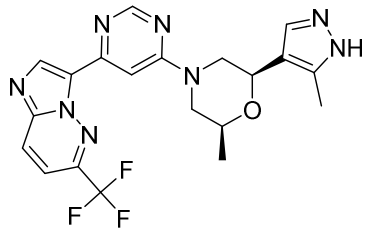
II-764



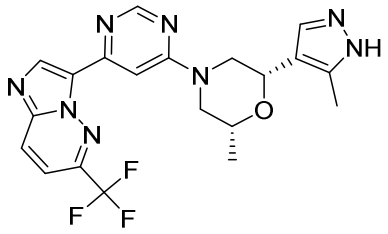
II-765



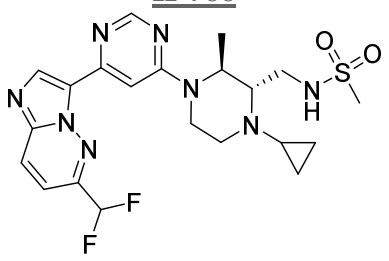
II-766



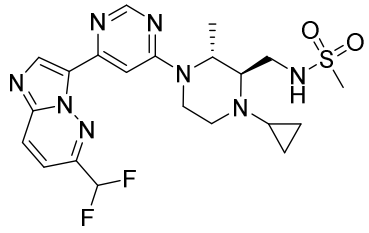
II-767



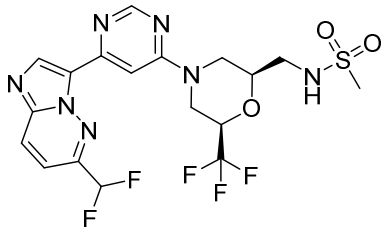
II-768



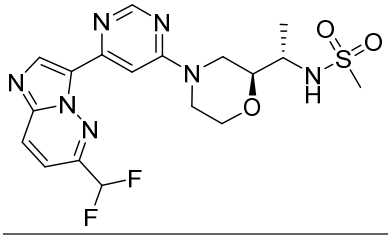
II-769



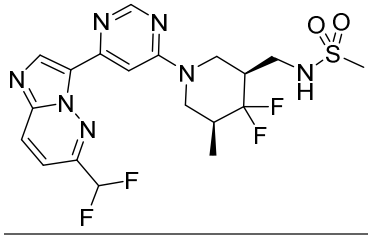
II-770



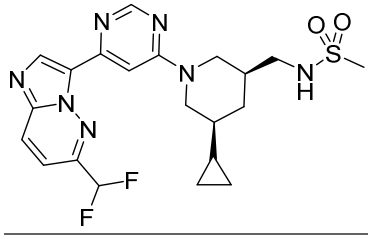
II-771



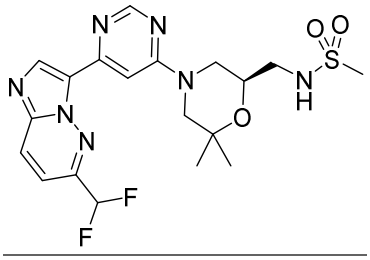
II-772



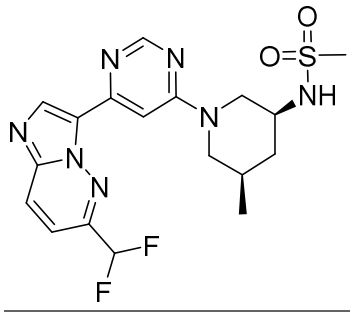
II-773



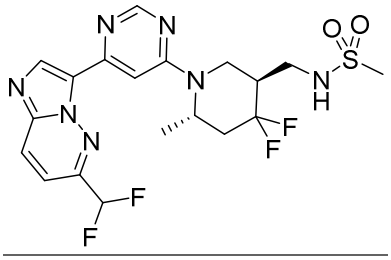
II-774



II-776



II-777



II-778

or a pharmaceutically acceptable salt thereof.

~~16~~17. A pharmaceutical composition comprising a compound according to any one of claims 1 to ~~15~~16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

~~17~~18. 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 ~~15~~16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

~~18~~19. A compound according to any one of claims 1 to ~~15~~16, 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 selected from 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.

~~19~~20. Use of the compound according to any one of claims 1 to ~~15~~16, 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 in a patient selected from 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.

~~20. The use of claim 19, 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.~~

21. The use of claim 20, 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.

22. The use of claim 20, wherein the autoimmune condition is rheumatoid arthritis, systemic lupus, multiple sclerosis, psoriasis, Sjögrens syndrome or transplant organ rejection.

23. The use of claim 20, wherein the metabolic condition is diabetes.

24. The use of claim 20, wherein the degenerative disease is osteoarthritis.

25. The use of claim 20, wherein the inflammatory condition is asthma, inflammatory bowel disease, or giant cell arteritis.

26. The use of claim 20, wherein the cardiovascular disease is an ischemic injury.

27. The use of claim 20, 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.

28. The use of claim 20, 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.

29. The use of claim ~~19~~20, wherein the ~~GCN2-mediated~~ disorder, disease, or condition is a cancer and wherein the compound is to be administered in conjunction with a second agent ~~is to be administered in conjunction with the medicament for the treatment of cancer~~.