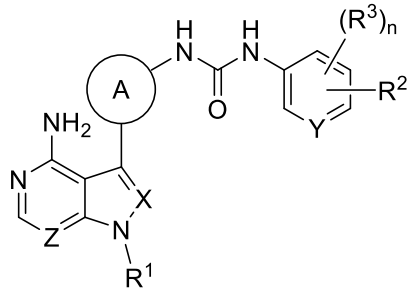
CLAIMS

1. A compound having the following Structure (I):



(I)

or a pharmaceutically acceptable salt, or stereoisomer thereof,wherein:

A is phenylene or pyridinylene, each of which is optionally substituted;

X is N or CR^4;

Y is N or CH;

Z is N;

R^1 is C_1-C_6 alkyl, C_1-C_6 hydroxylalkyl, C_3-C_{10} cycloalkyl, or 3-10 membered heterocyclyl, each of which is optionally substituted;

R^2 is a 3-10 membered heterocyclyl, 3-10 membered heterocyclylalkyl, 3-10 membered heterocyclylalkenyl, 3-10 membered heterocyclylcarbonyl, 3-10 membered heterocyclyloxy, or 5-6 membered heteroaryl, each of which is optionally substituted;

R^3 is, at each occurrence, independently halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl;

R^4 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl; and

n is 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein A is unsubstituted or substituted with one or more halo substituents.

3. The compound of any one of claims 1-2, wherein X is CR^4.

4. The compound of any one of claims 1-3, wherein R^4 is H or C_1-C_6 alkyl.

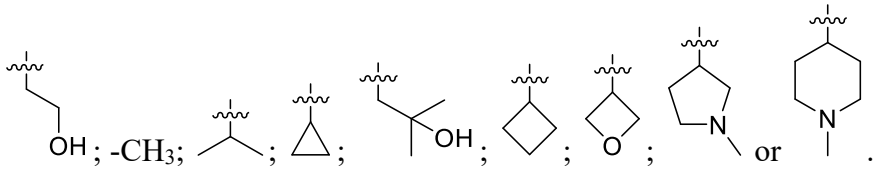
5. The compound of any one of claims 1-4, wherein R^4 is H.

6. The compound of any one of claims 1-2, wherein X is N.

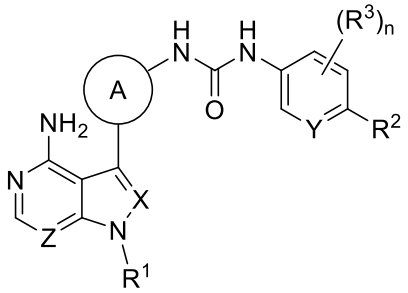
7. The compound of any one of claims 1-6, wherein R^1 is methyl, iso-propyl, cyclopropyl, cyclobutyl, oxetanyl, pyrrolidinyl, azetidinyl or piperidinyl.

8. The compound of any one of claims 1-7, wherein R^1 is unsubstituted or substituted with one or more substituents selected from halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl.

9. The compound of any one of claims 1-8, wherein R^1 has one of the following structures:



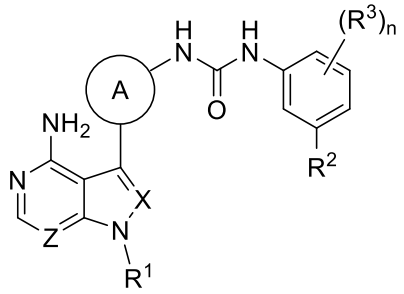
10. The compound of any one of claims 1-9, wherein the compound has the following Structure (Ia):



(Ia)

or a pharmaceutically acceptable salt, or stereoisomer thereof.

11. The compound of any one of claims 1-9, wherein the compound has the following Structure (Ib):

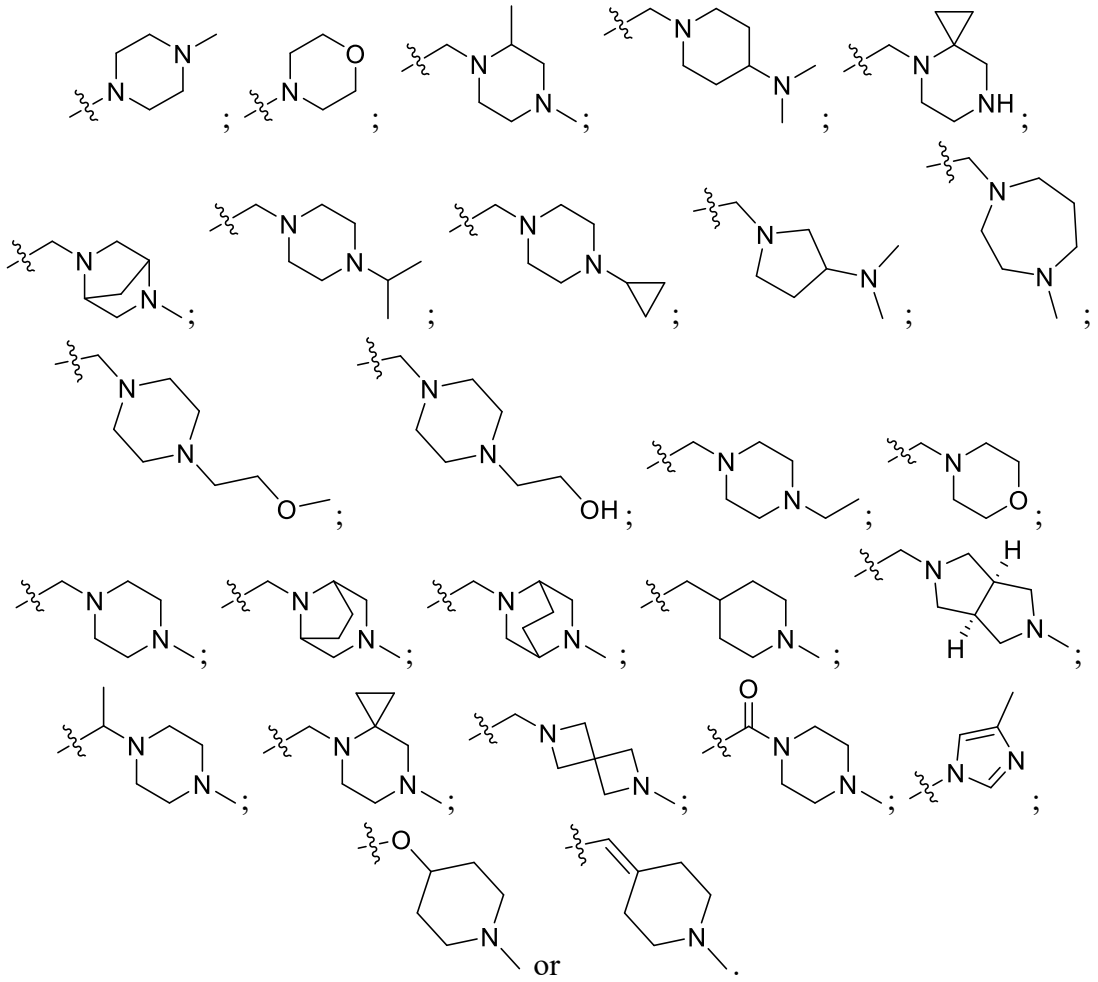


(Ib)

or a pharmaceutically acceptable salt, or stereoisomer thereof.

12. The compound of any one of claims 1-11, wherein R^2 is morpholino or piperazinyl.

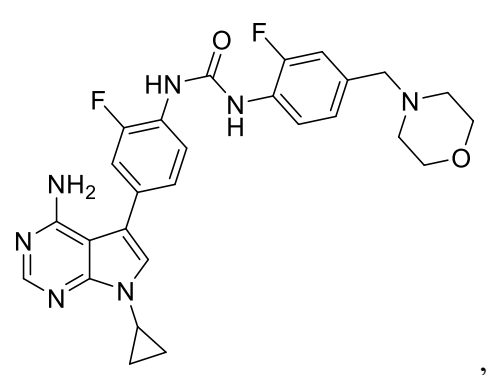
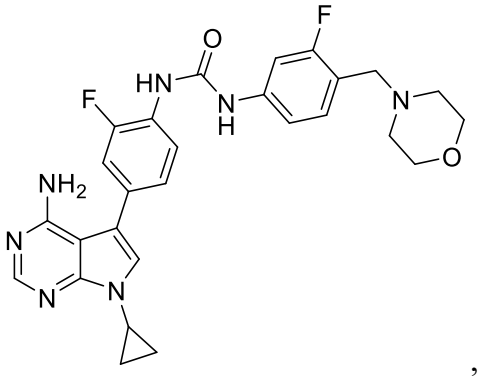
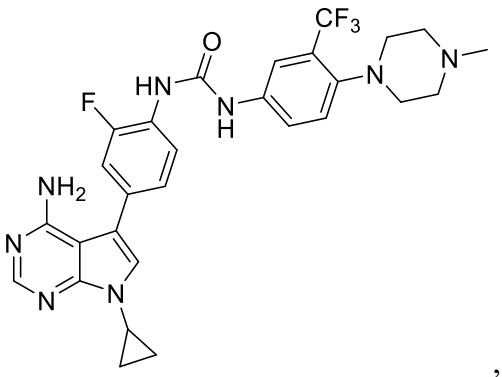
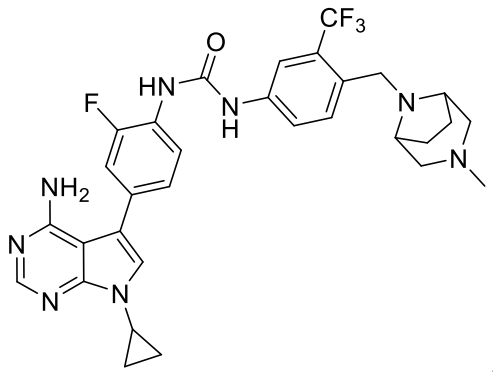
13. The compound of any one of claims 1-11, wherein R^2 has one of the following structures:

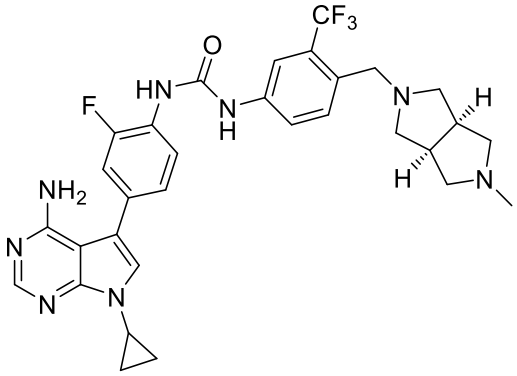
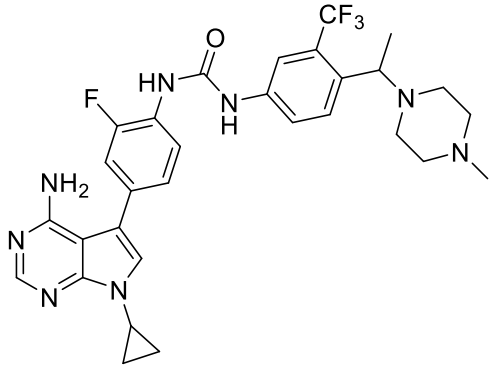
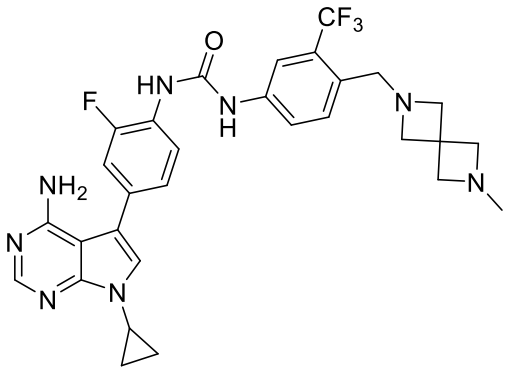
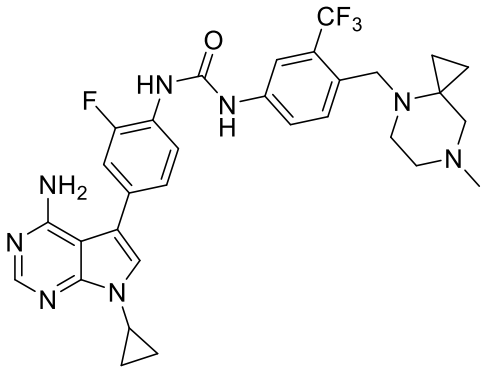
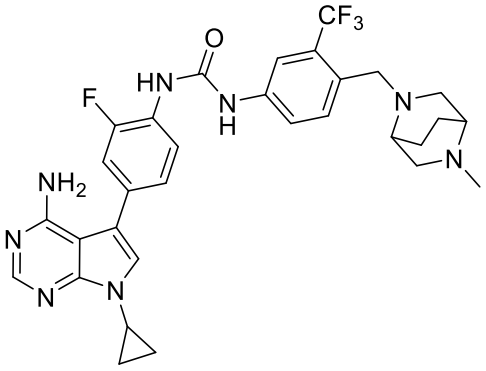
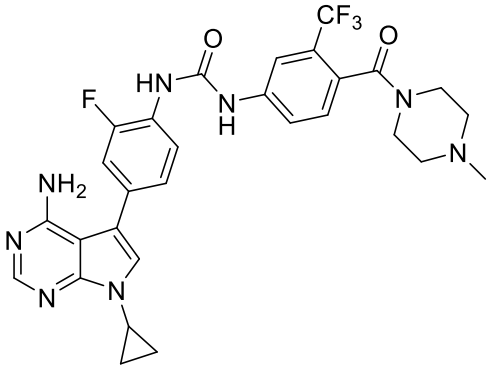
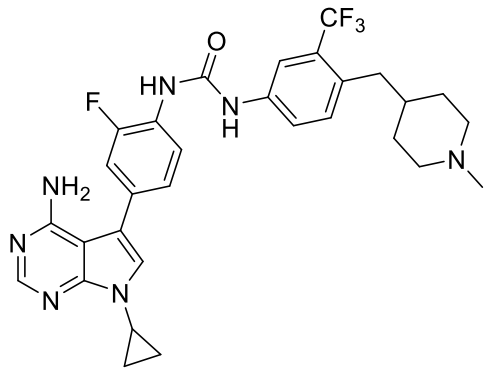
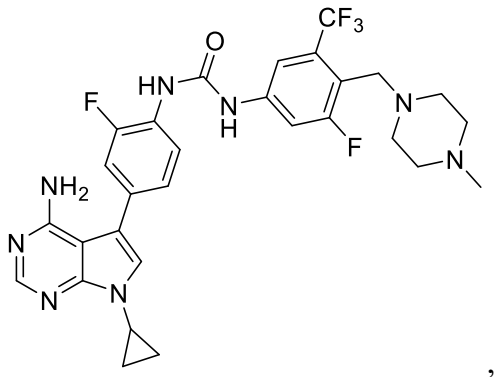


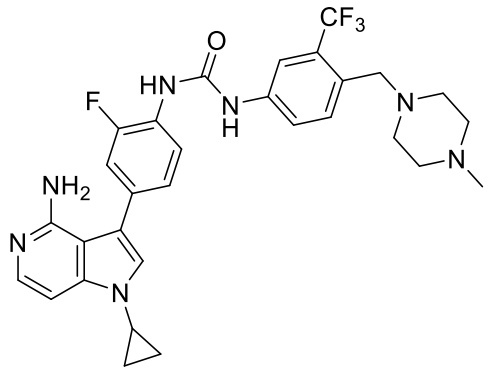
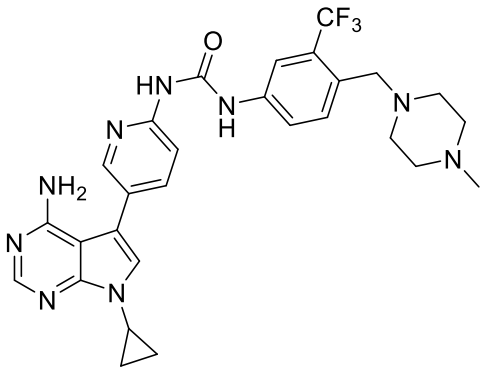
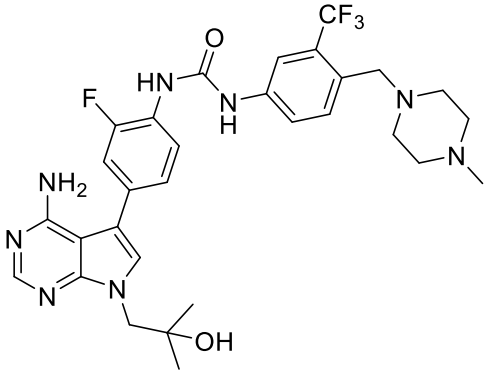
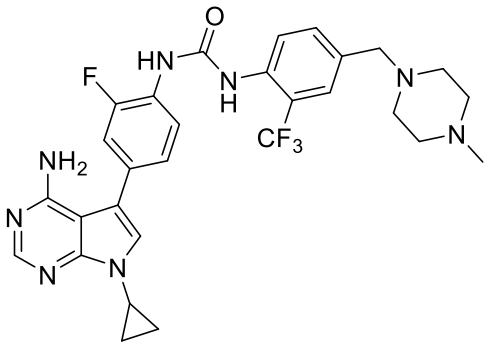
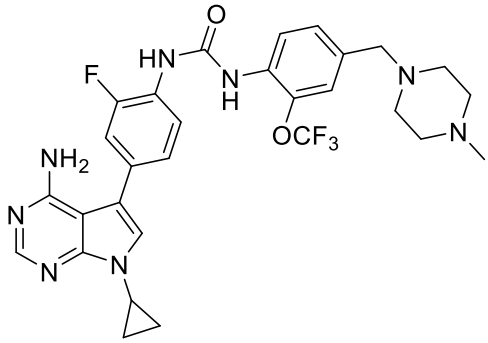
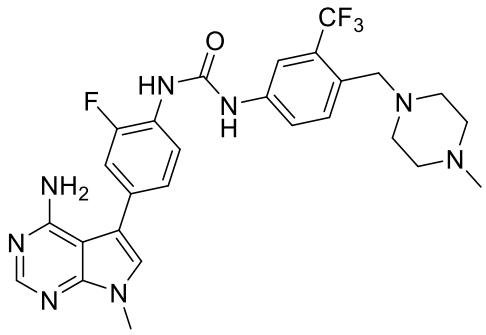
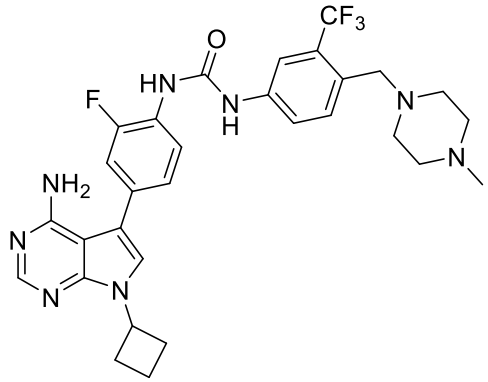
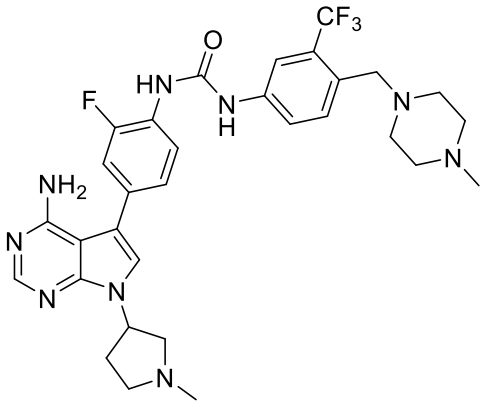
14. The compound of any one of claims 1-13, wherein n is 1 or 2.

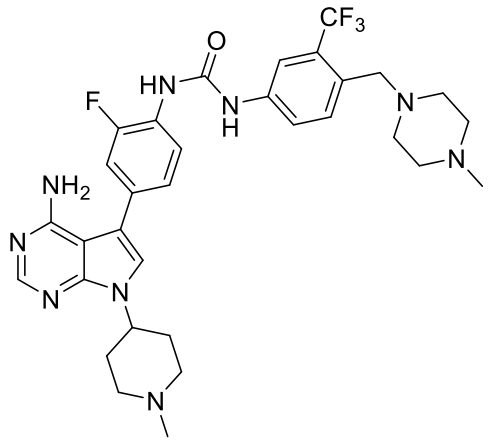
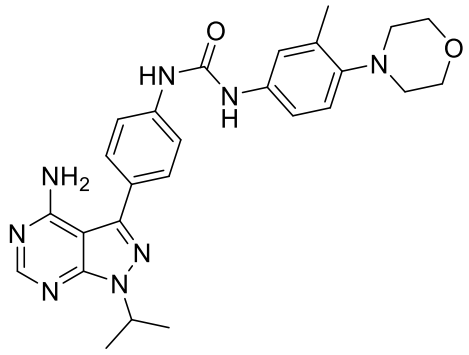
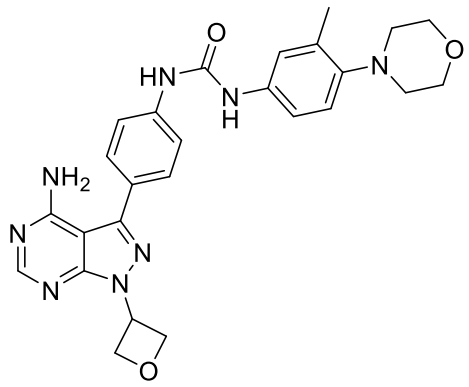
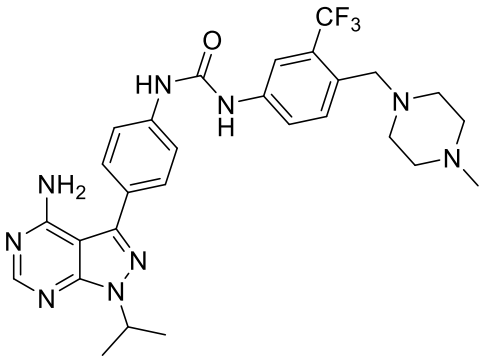
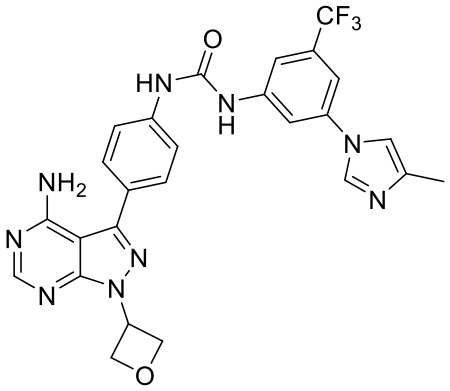
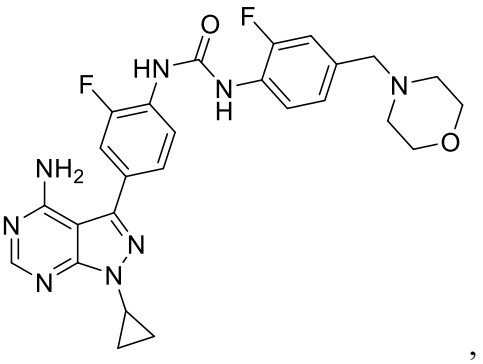
15. The compound of any one of claims 1-14, wherein R^3 is methyl, chloro, fluoro, cyano, difluoromethyl, trifluoromethyl, methoxy, trifluoromethoxy, or cyclopropyl.

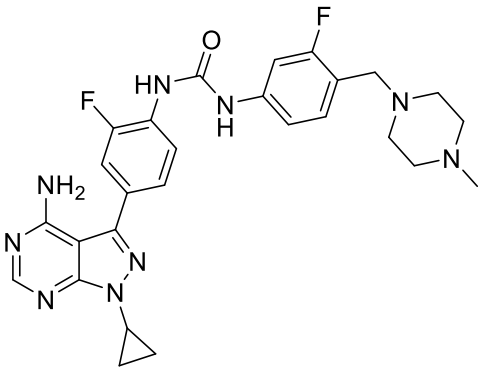
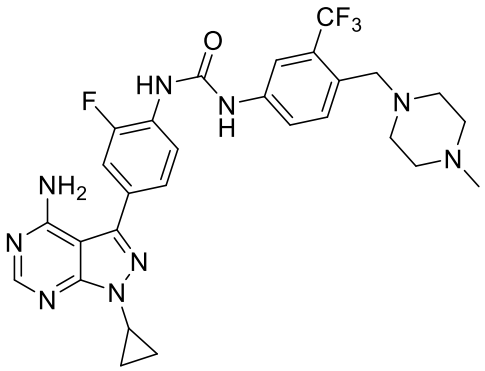
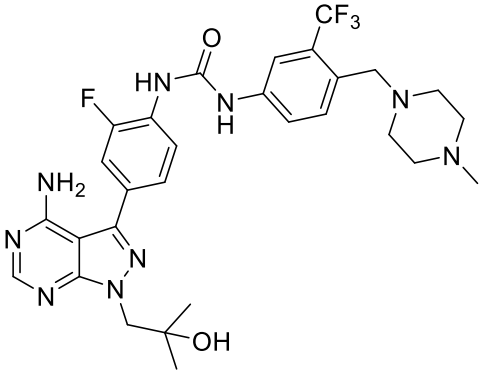
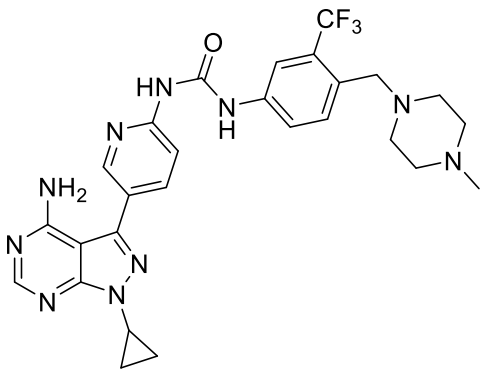
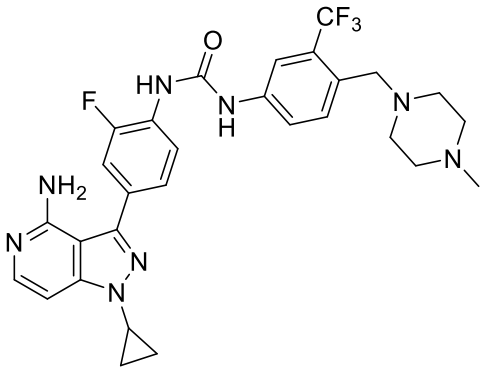
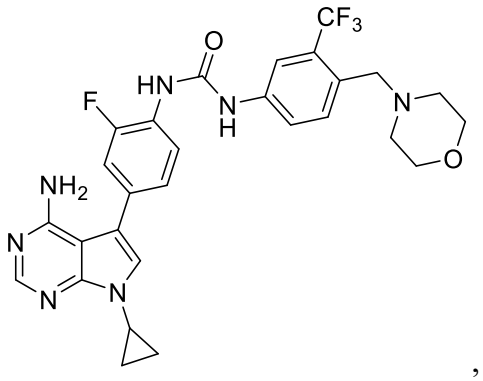
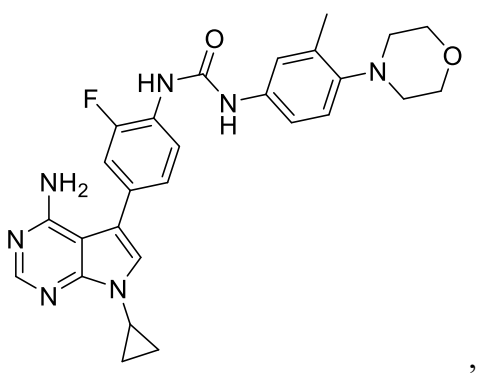
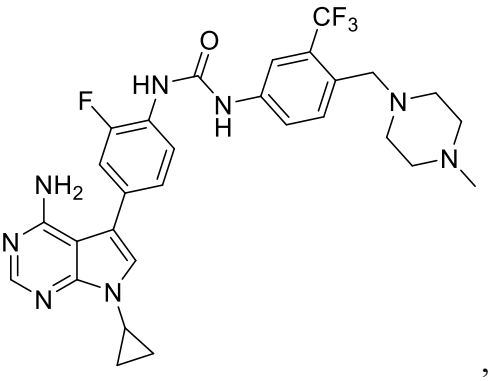
16. A compound having one of the following structures:

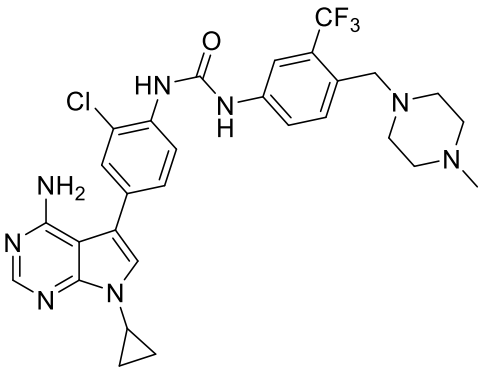
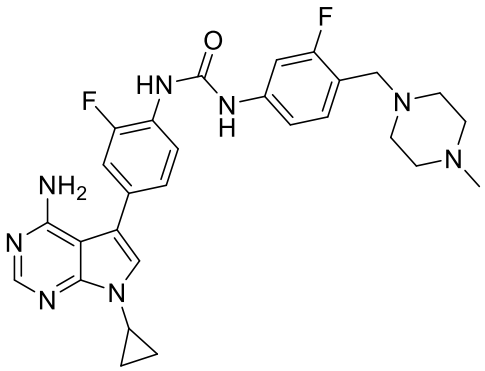
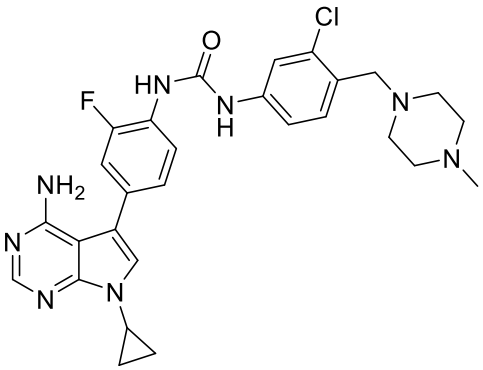
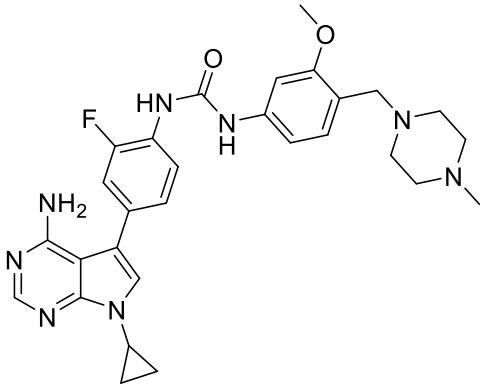
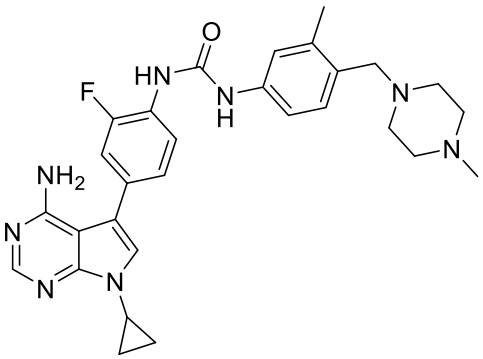
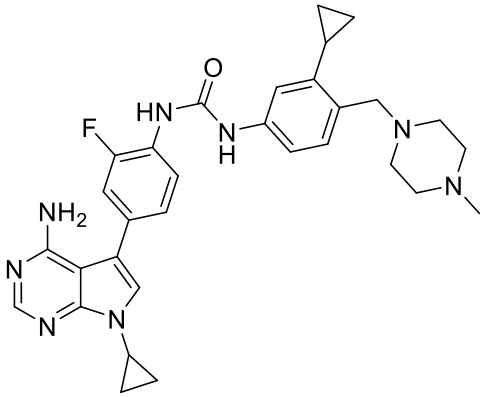
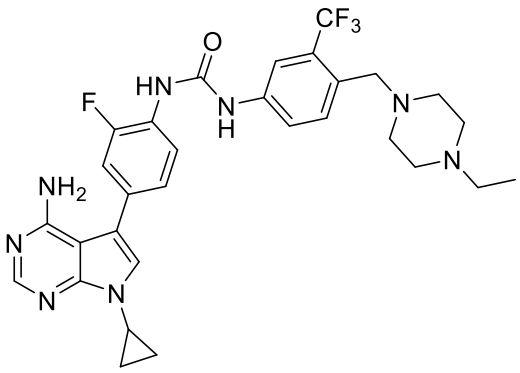
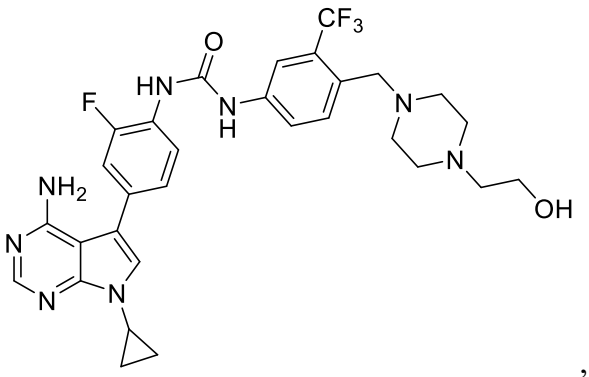

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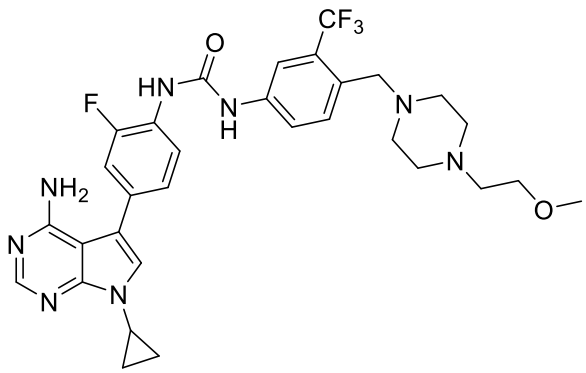
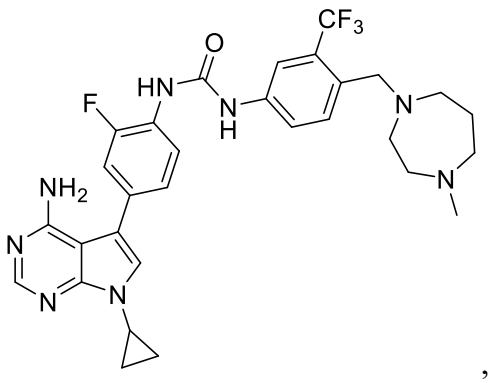
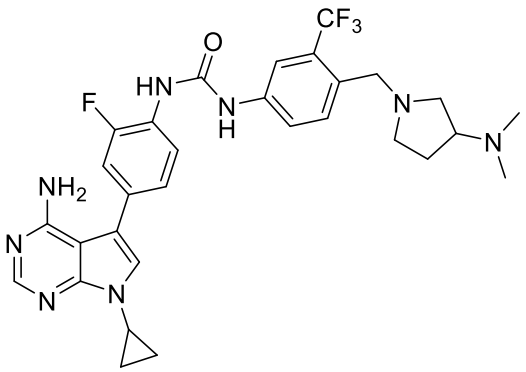
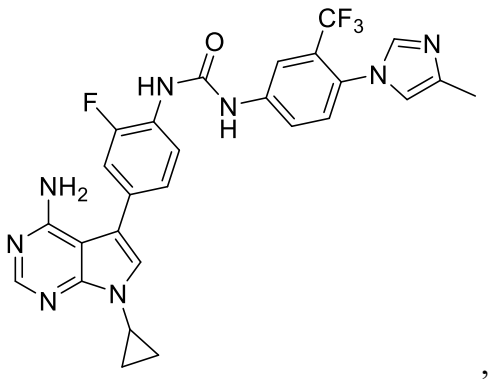
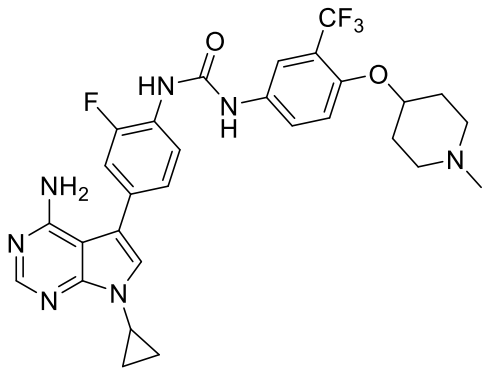
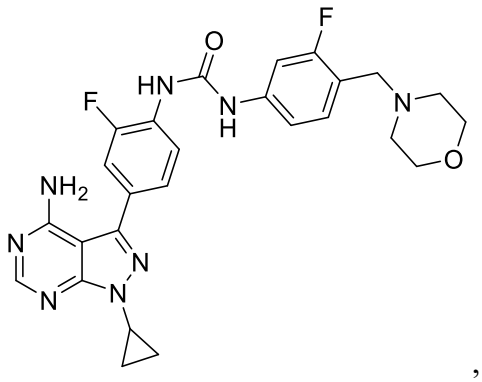
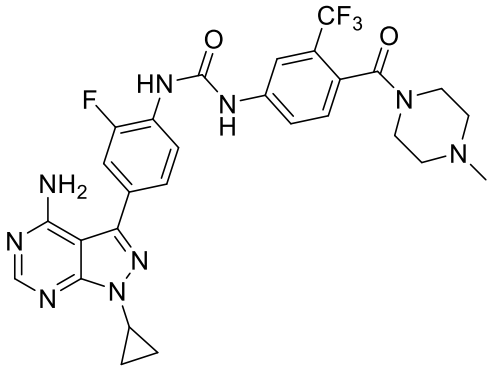
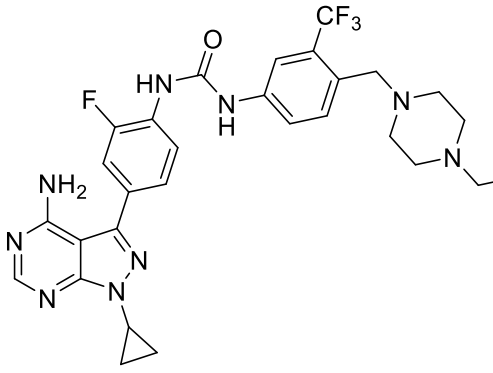

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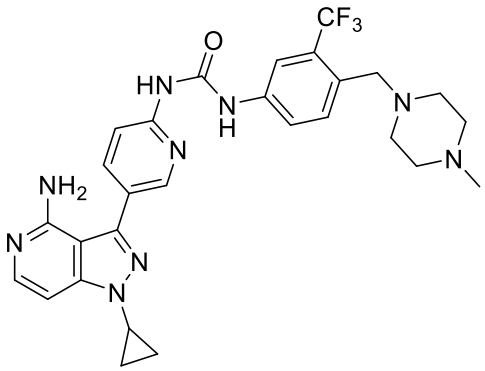
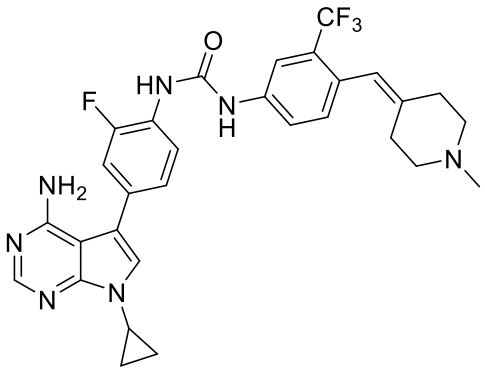
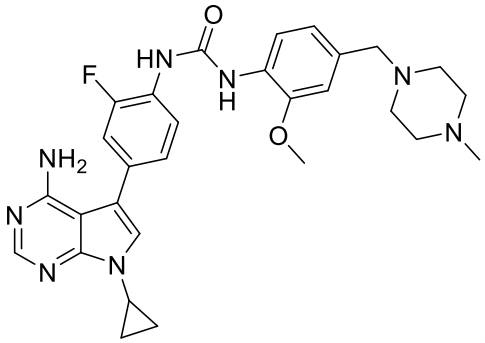
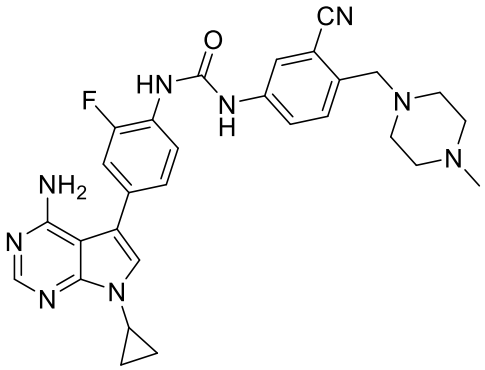
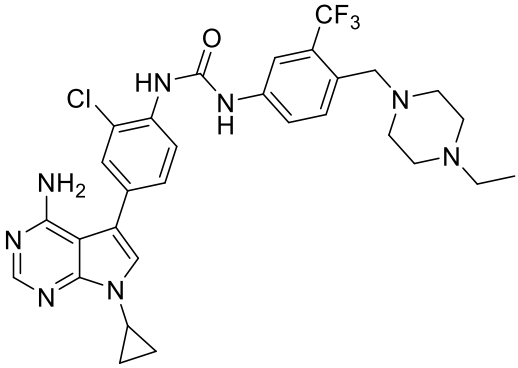
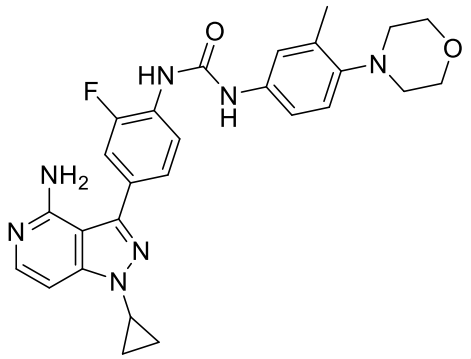
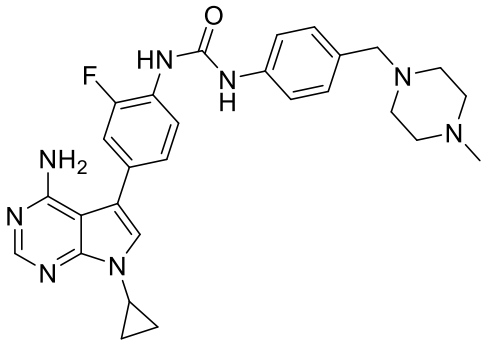
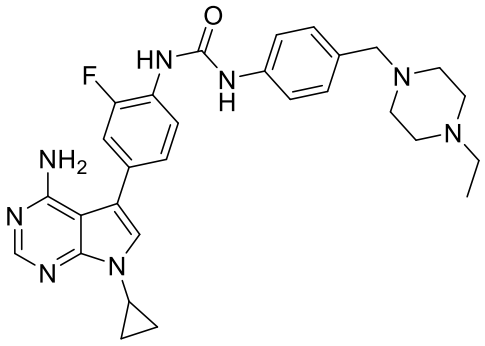

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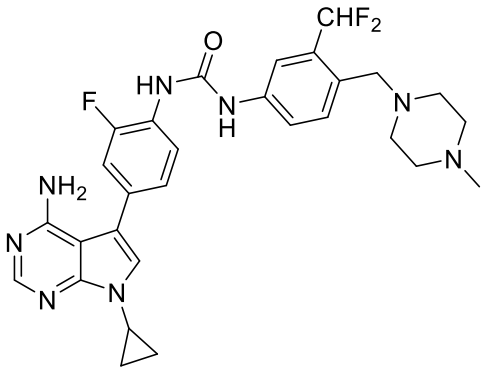
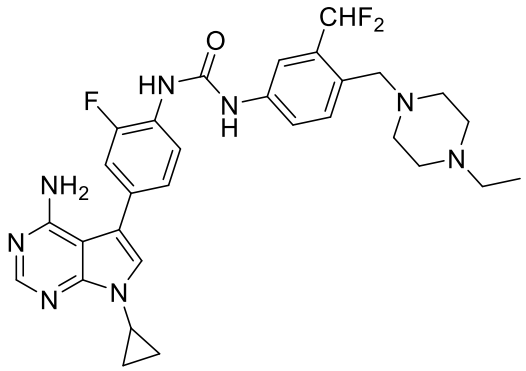
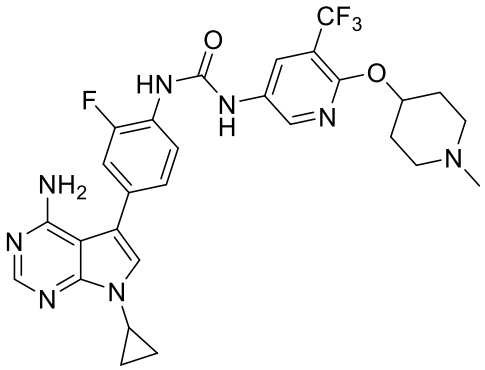
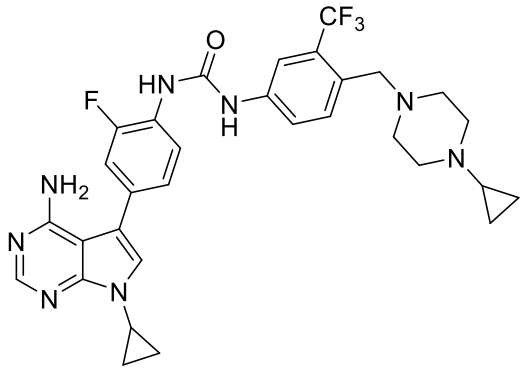
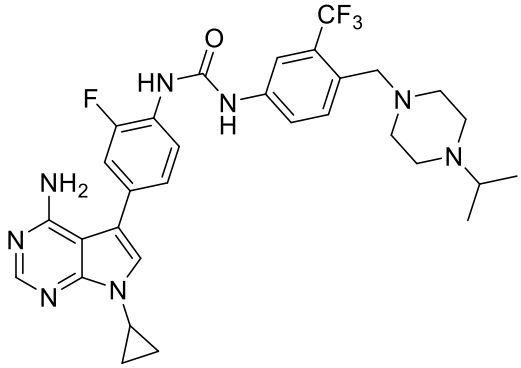
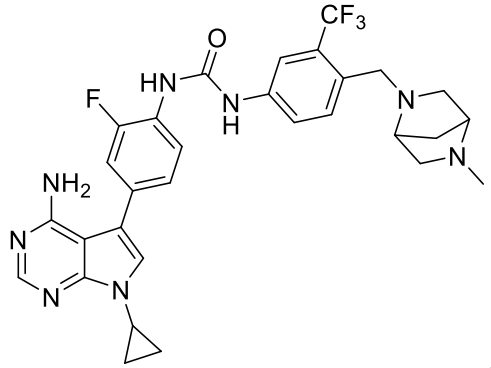
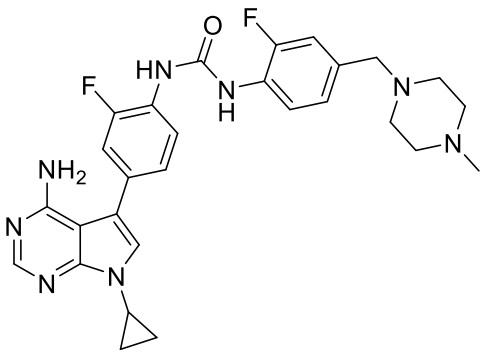
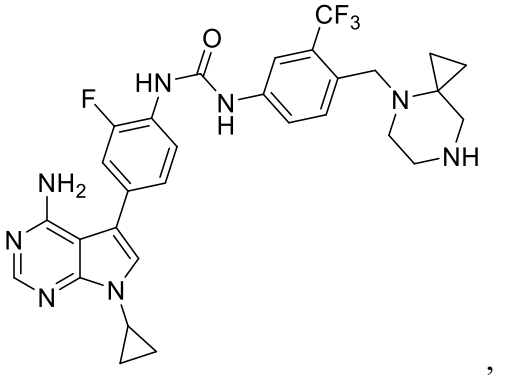

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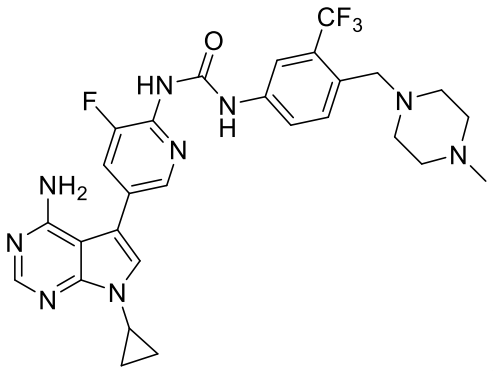
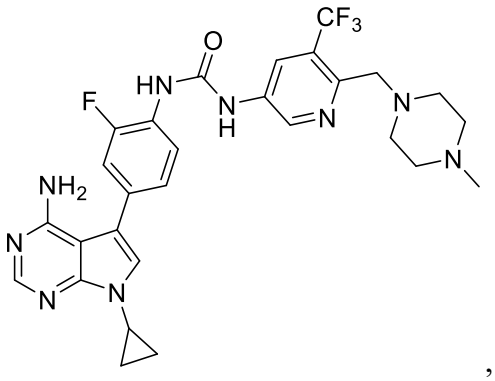
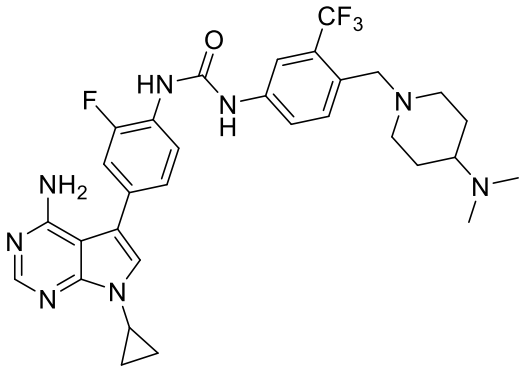
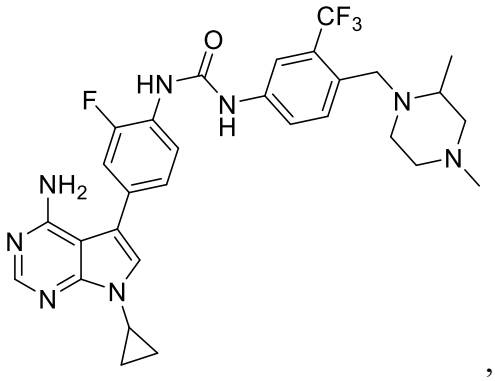
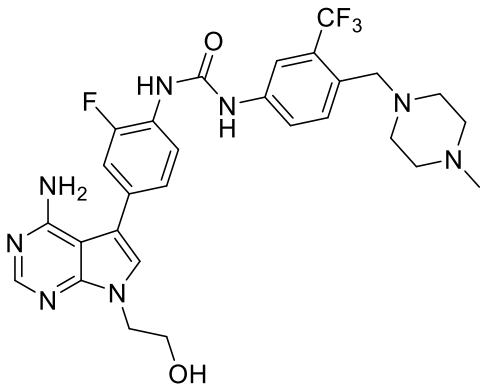
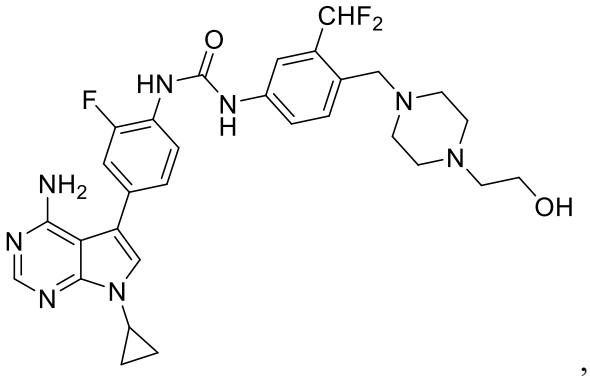

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or a pharmaceutically acceptable salt, or stereoisomer thereof.

17. The compound of any one of claims 1-16, wherein the compound is a modulator of the NLRP3 inflammasome, an inhibitor of NEK7, or both.

18. A pharmaceutical composition comprising the compound of any one of claims 1-17, and a pharmaceutically acceptable carrier, diluent, or excipient.

19. Use of a therapeutically effective amount of a compound of any one of claims 1-17, or the pharmaceutical composition of claim 18 in the manufacture of a medicament for treating a NLRP3-mediated disorder in a subject in need thereof, wherein the disorder is selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, allergy, asthma, pancreatitis, multi-organ failure, kidney diseases, cancer, transplantation, erythrocyte deficiency, graft rejection, lung injuries, respiratory diseases, ischemic conditions, and combinations thereof.

20. The use of claim 19, wherein the disorder is selected from type II diabetes, atherosclerosis, Alzheimer's disease, fatty liver, metabolic syndrome, asthma, psoriasis, obesity, acute and chronic tissue damage caused by infection, gout, arthritis, macular degeneration, enteritis, hepatitis, peritonitis, silicosis, UV-induced skin sunburn, contact hypersensitivity, sepsis, cancer, neurodegenerative disease, multiple sclerosis, Muckle-Wells syndrome, and combinations thereof.