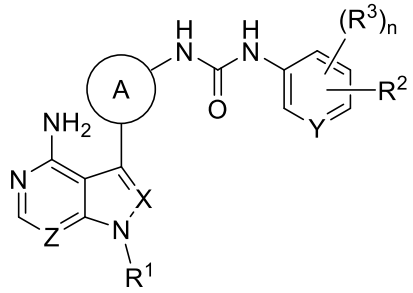
CLAIMS

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



(I)

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

A is C_6-C_{10} arylene, C_3-C_{10} cycloalkylene, 3-10 membered heterocyclylene, or 5-6 membered heteroarylene;

X is N or CR^4;

Y is N or CH;

Z is N or CH;

R^1 is C_1-C_6 alkyl, C_1-C_6 alkynyl, C_1-C_6 hydroxylalkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkoxyalkyl, C_3-C_{10} cycloalkyl, or 3-10 membered heterocyclyl;

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, or

R^2 joins with an occurrence of R^3 attached to a carbon adjacent to a carbon to which R^2 is attached to form a C_3-C_8 cycloalkyl;

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 phenylene or pyridinylene.

3. The compound of any one or claims 1-2, wherein A is unsubstituted or substituted with one or more halo substituents.

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

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

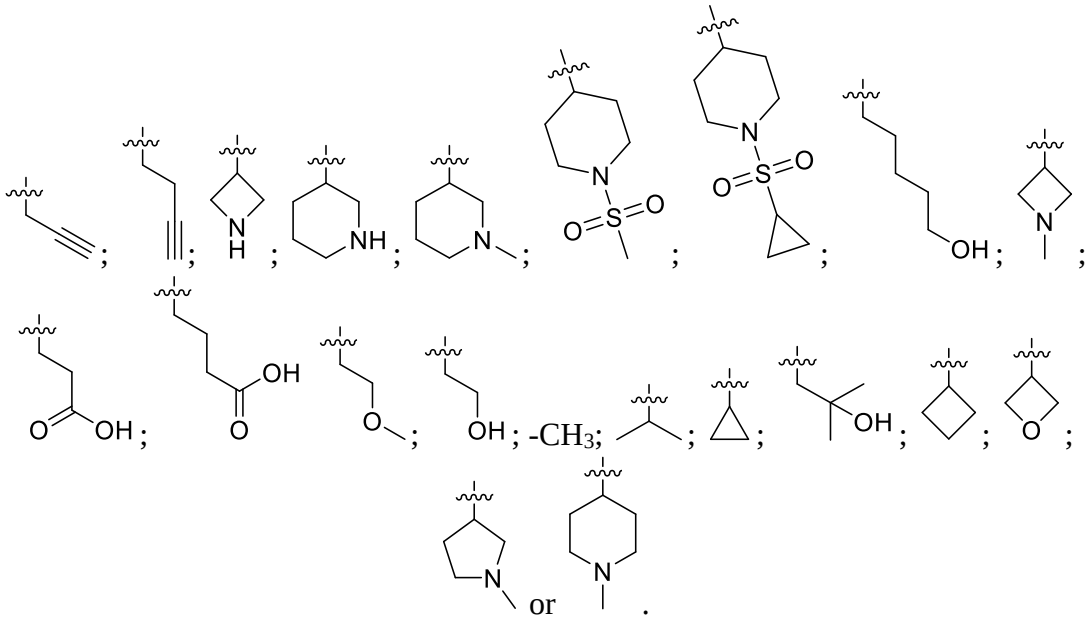
6. The compound of any one of claims 1-5, wherein R^4 is H.

7. The compound of any one of claims 1-3, wherein X is N.

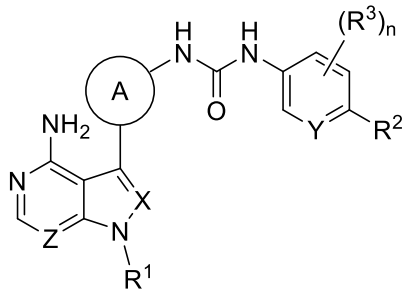
8. The compound of any one of claims 1-7, wherein R^1 is methyl, iso-propyl, cyclopropyl, cyclobutyl, oxetanyl, pyrrolidinyl, azetidinyl or piperidinyl.

9. The compound of any one of claims 1-8, 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, $-S(O)_2CH_3$, $-S(O)_2$cyclopropyl, or C_3-C_8 cycloalkyl.

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



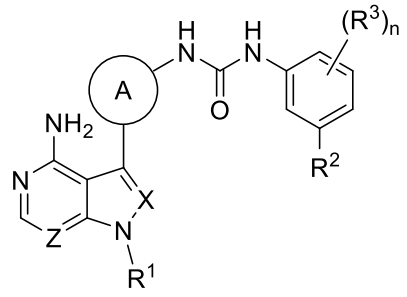
11. The compound of any one of claims 1-10, wherein the compound has the following Structure (Ia):



(Ia)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

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

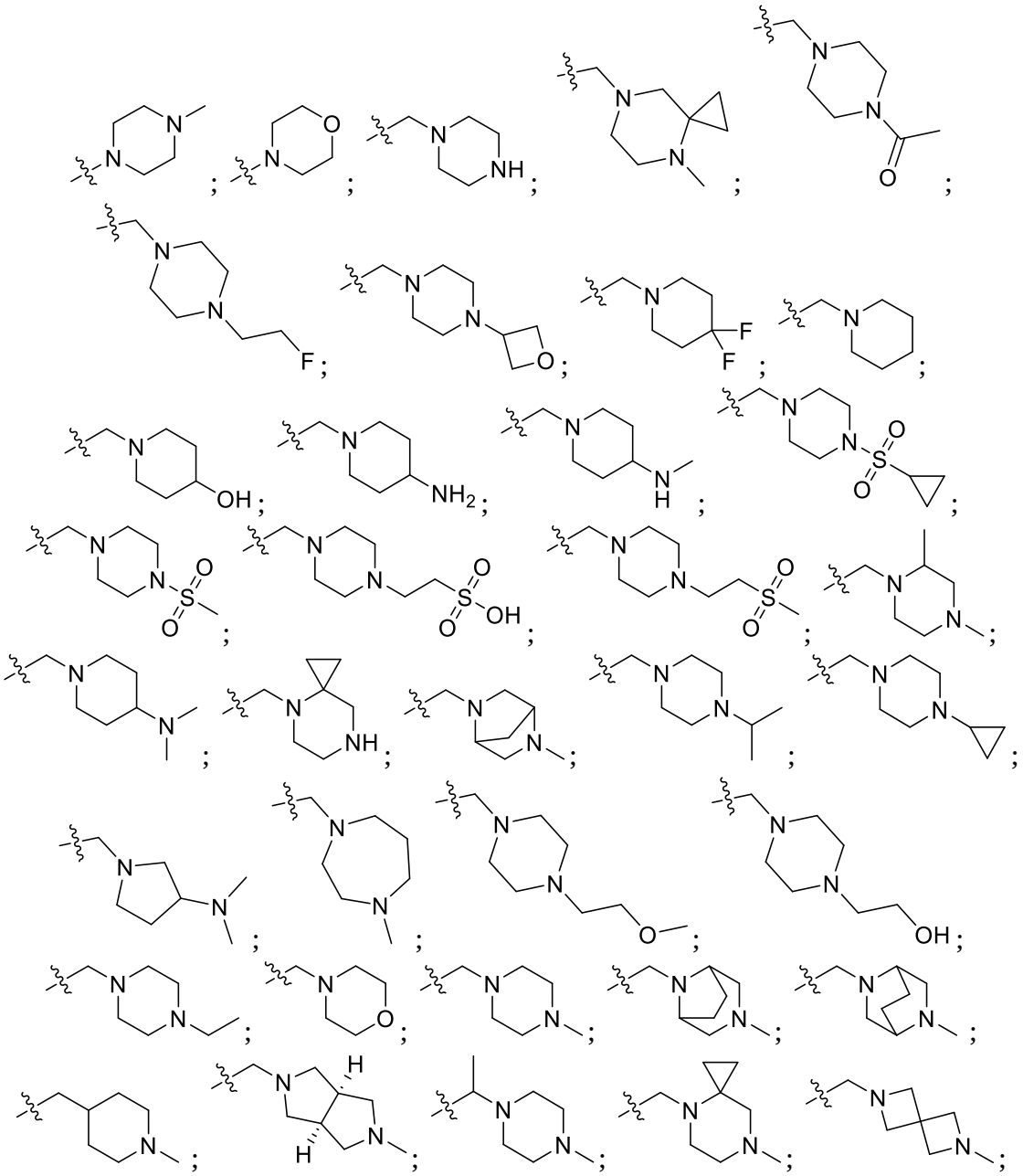


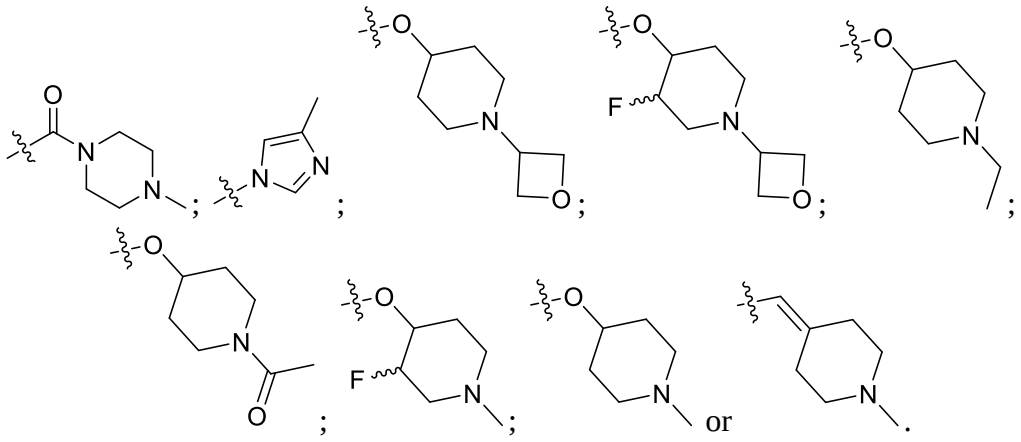
(Ib)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

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

14. The compound of any one of claims 1-12, wherein R^2 has one of the following structures:

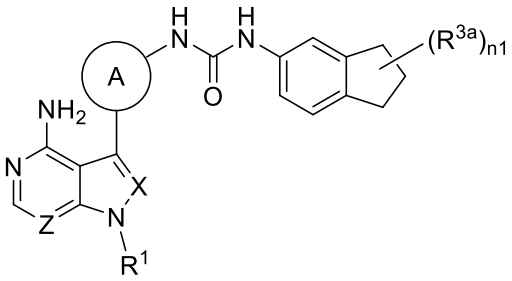




15. The compound of any one of claims 1-14, wherein n is 1 or 2.

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

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



(Ic)

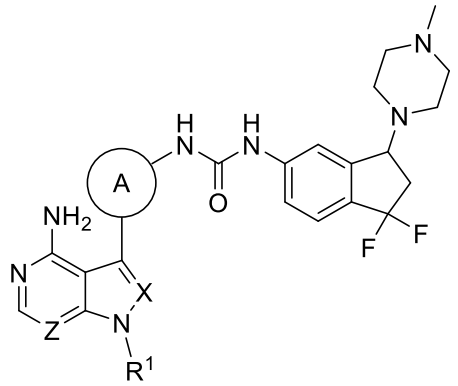
or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof, wherein:

R^{3a} is halo or 3-10 membered heterocyclyl; and

n1 is 1, 2, or 3.

18. The compound of claim 17, wherein R^{3a} is fluoro or piperazinyl.

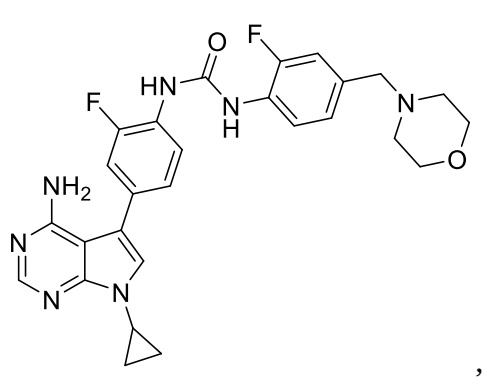
19. The compound of any one of claims 17-18, wherein the compound has the following Structure (Ic1):



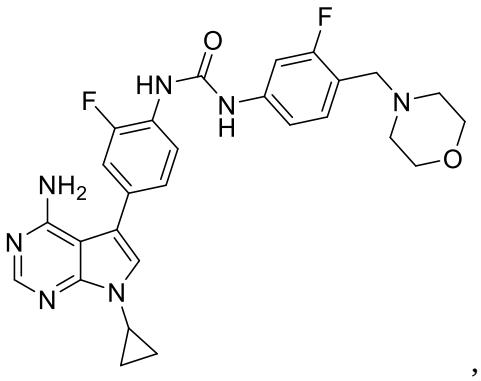
(Ic1)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

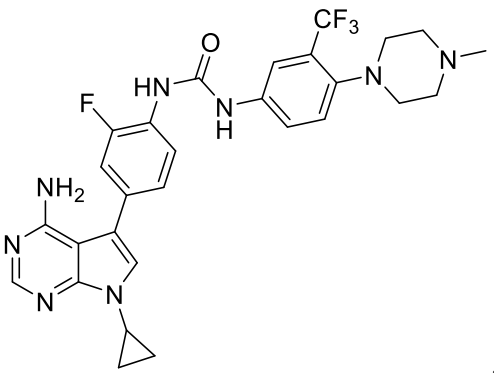
20. A compound having one of the following structures:



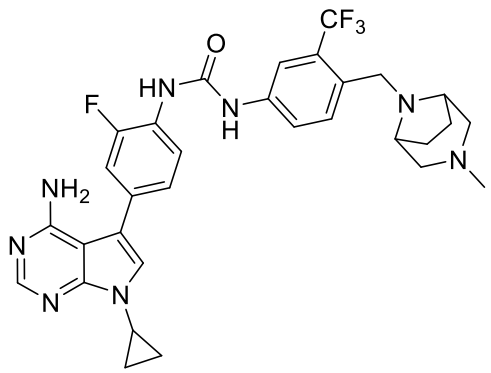
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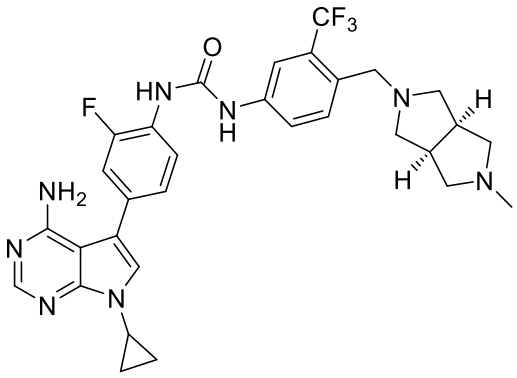
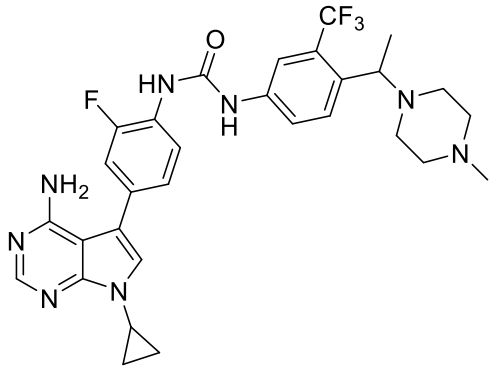
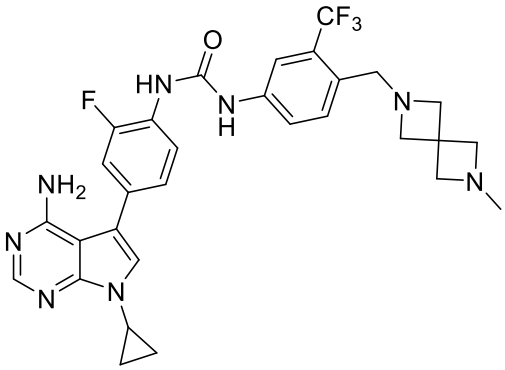
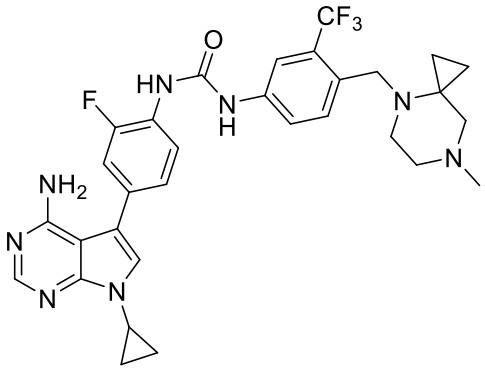
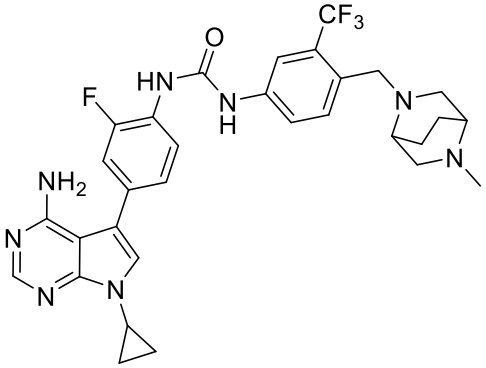
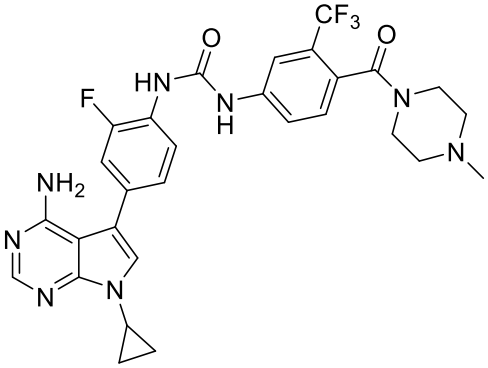
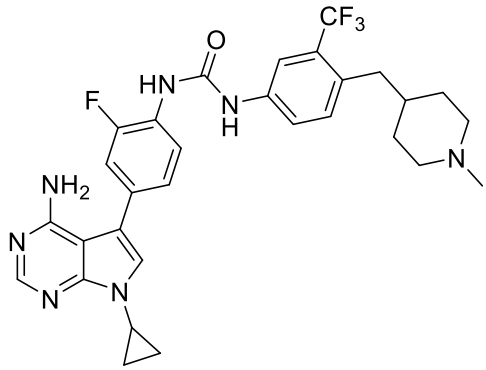
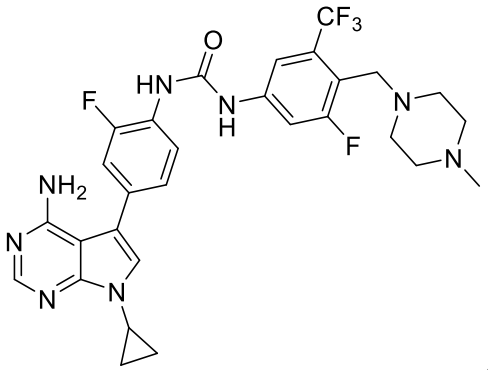
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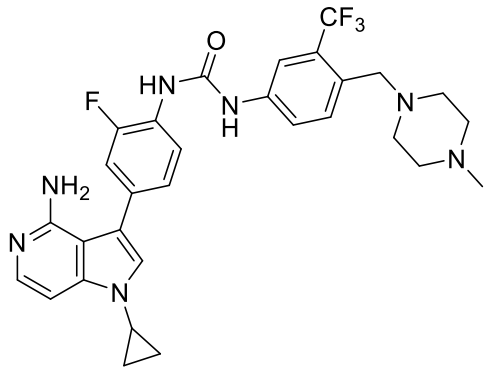
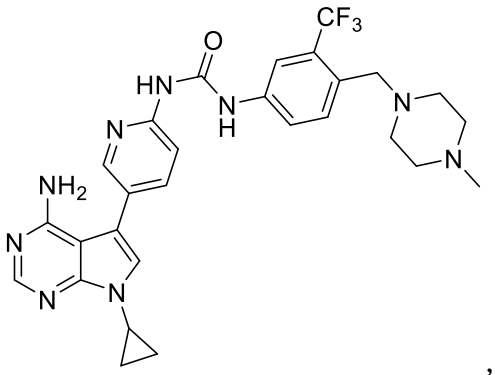
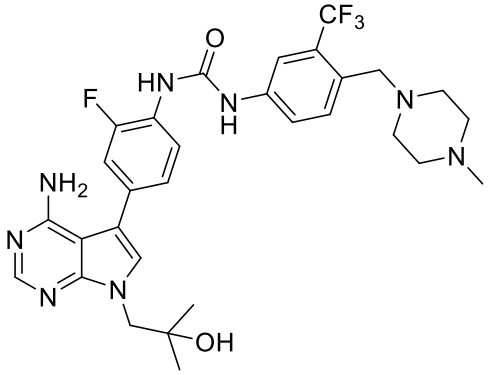
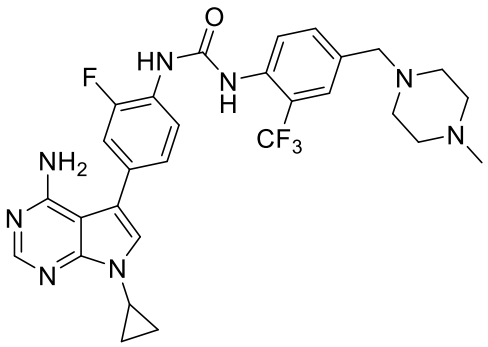
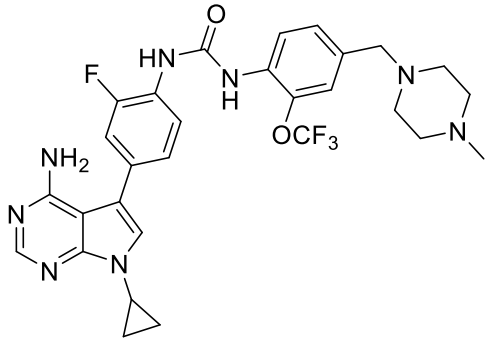
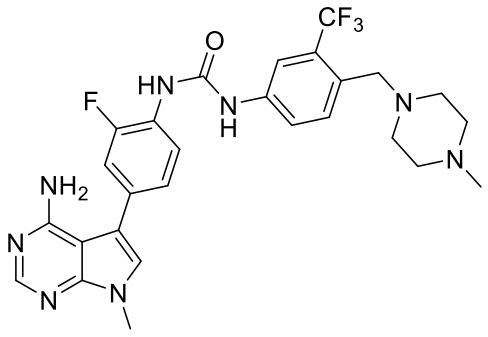
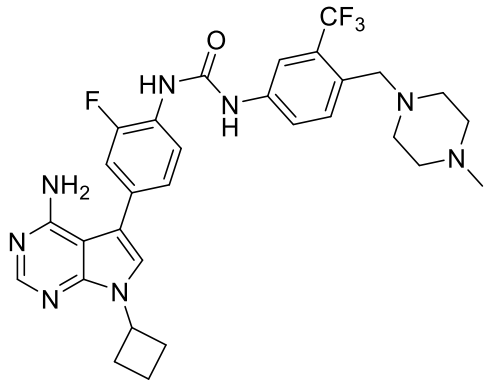
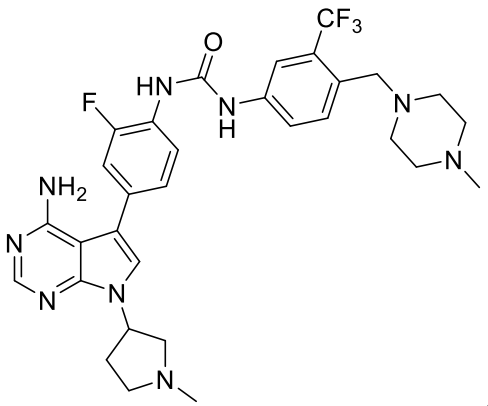


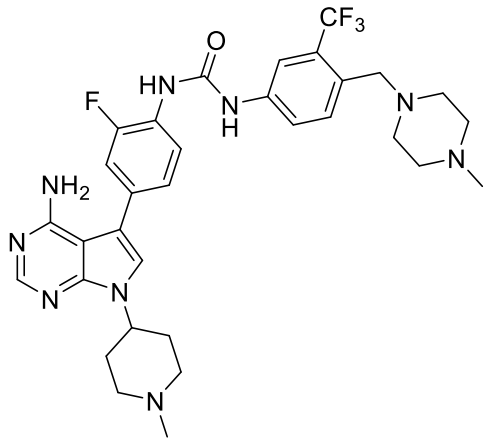
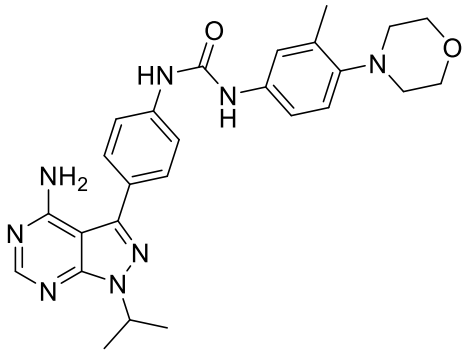
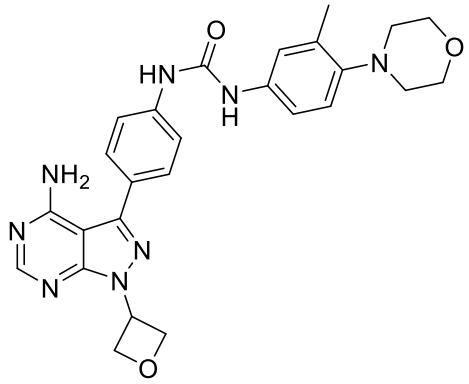
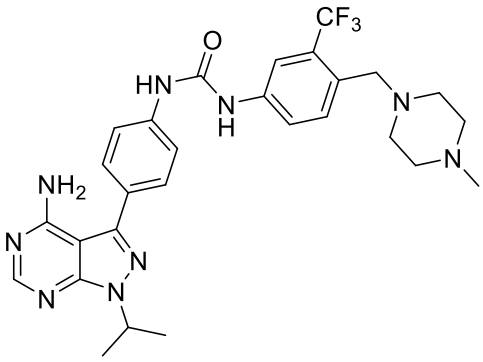
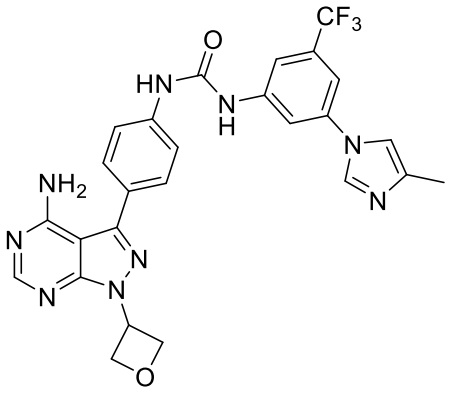
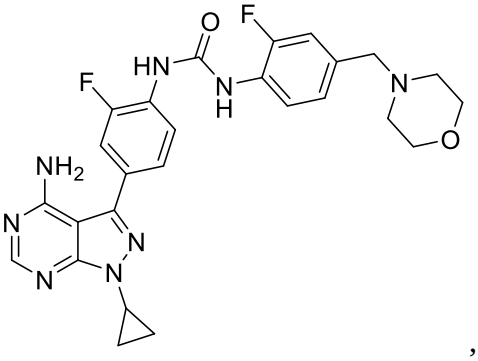
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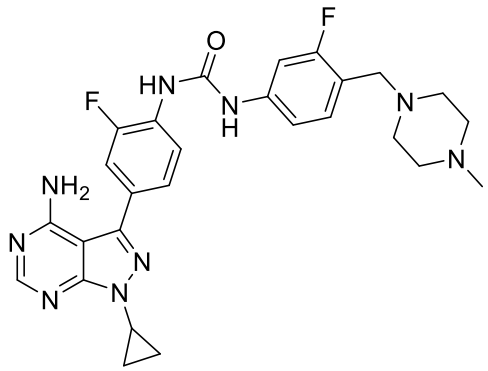
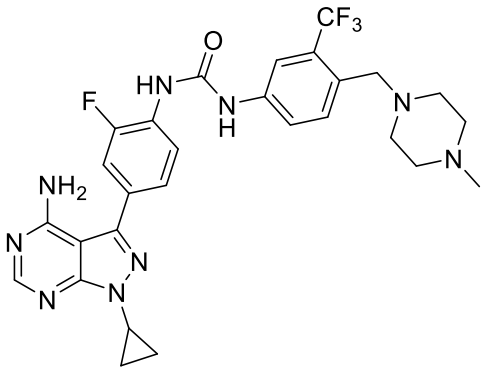
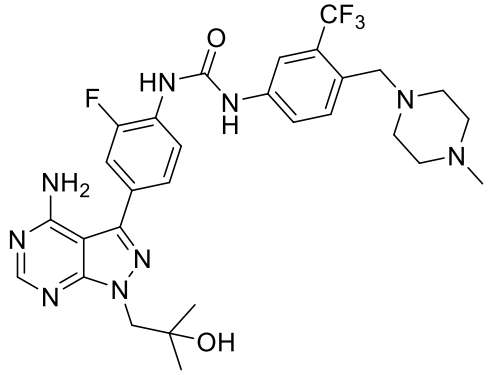
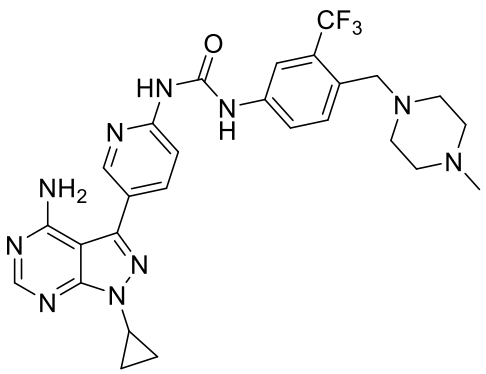
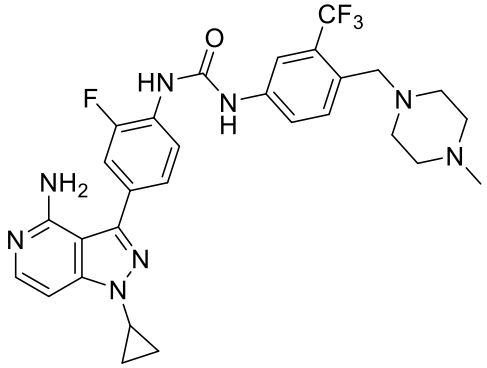
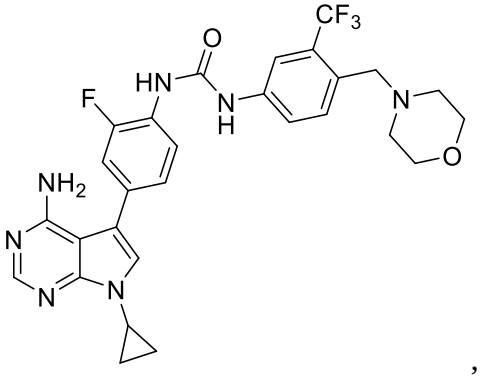
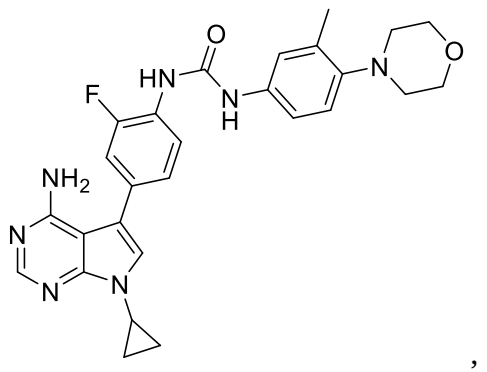
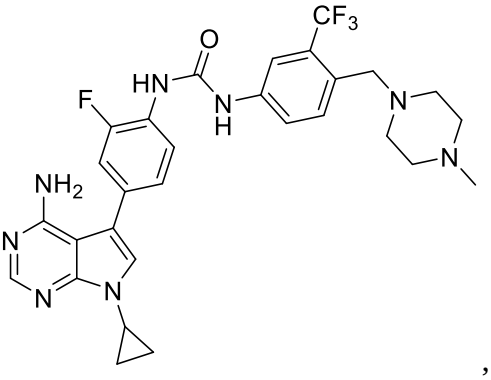


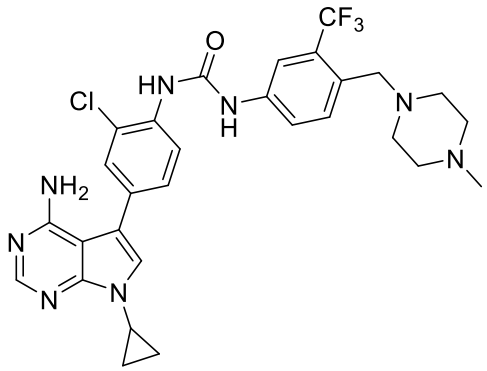
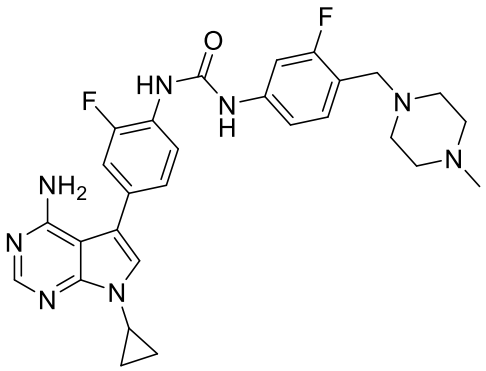
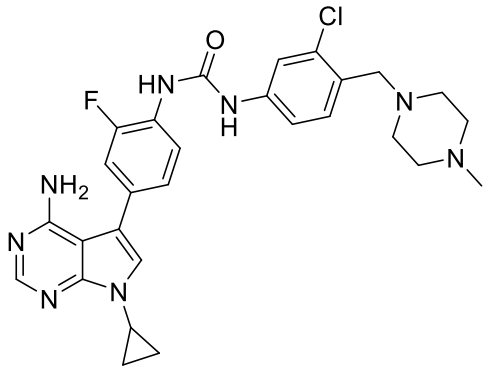
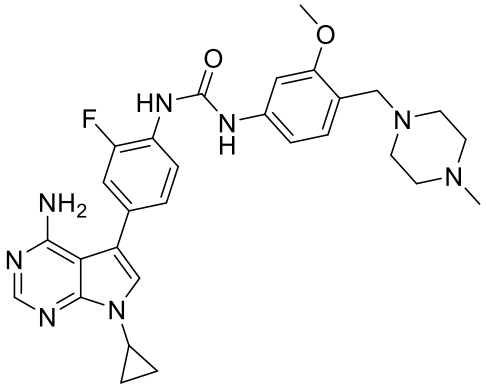
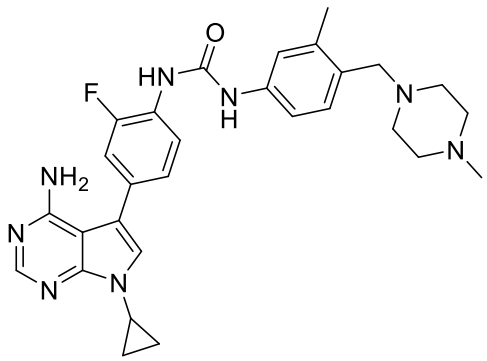
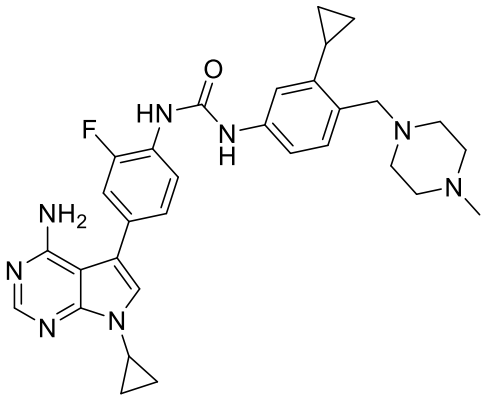
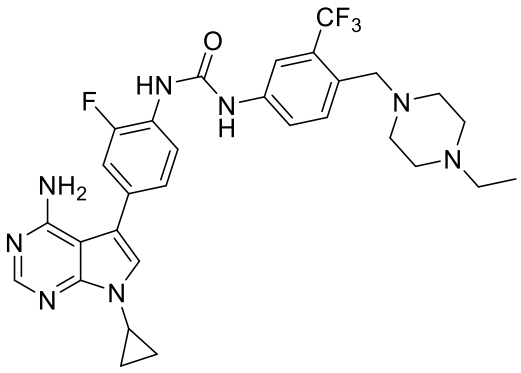
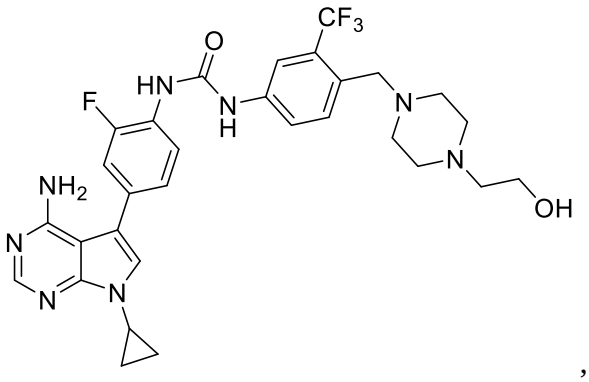
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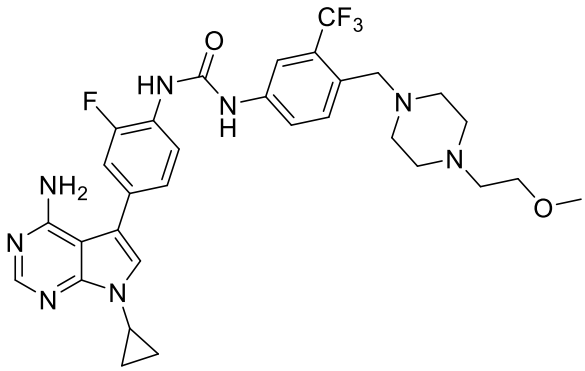
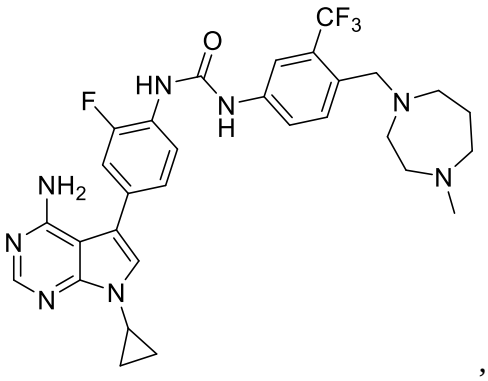
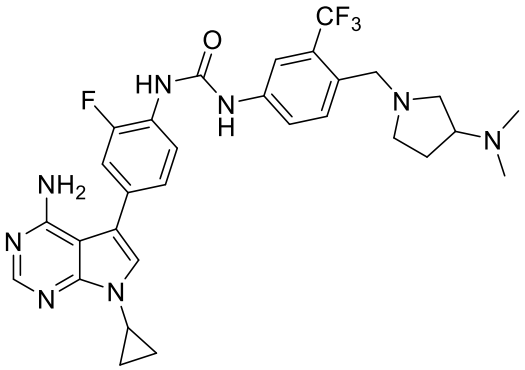
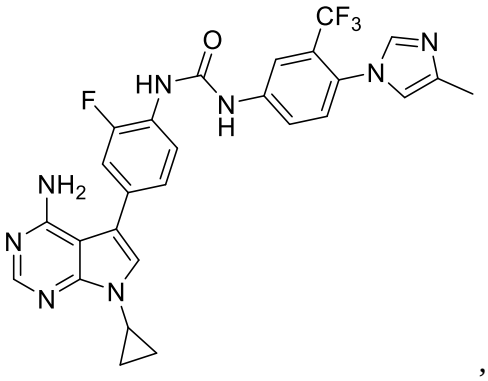
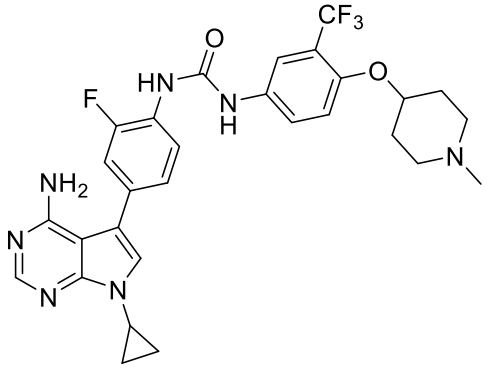
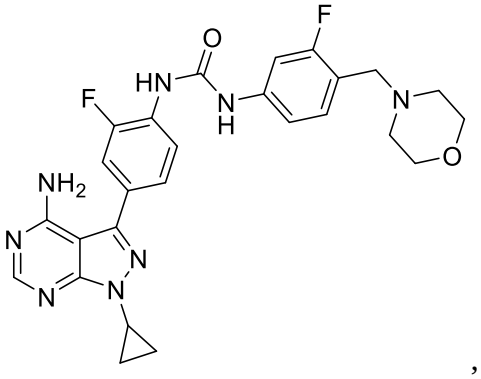
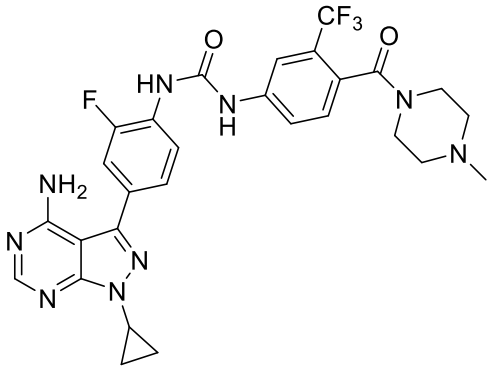
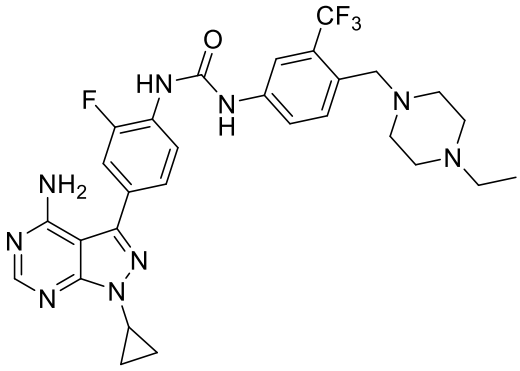

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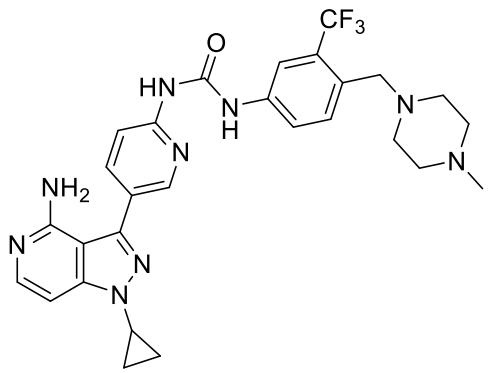
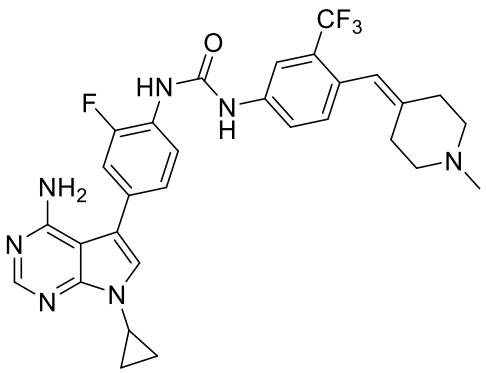
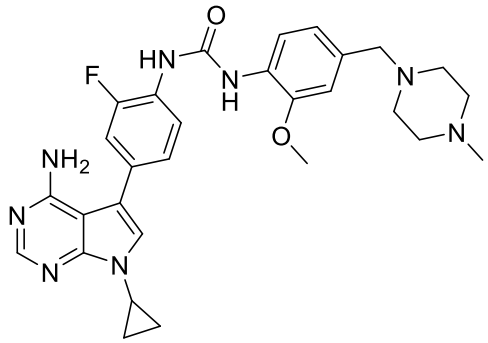
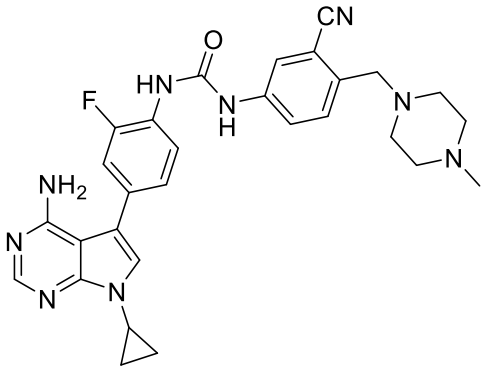
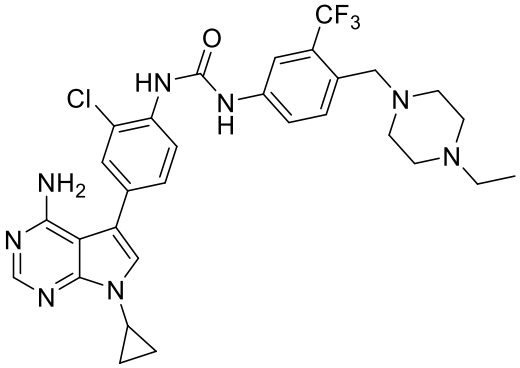
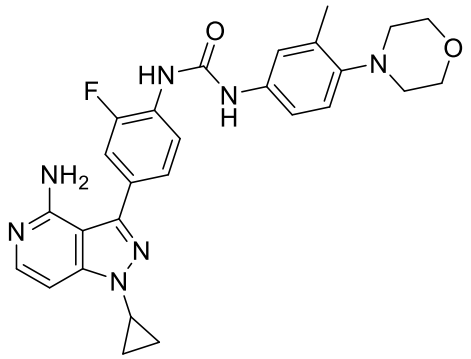
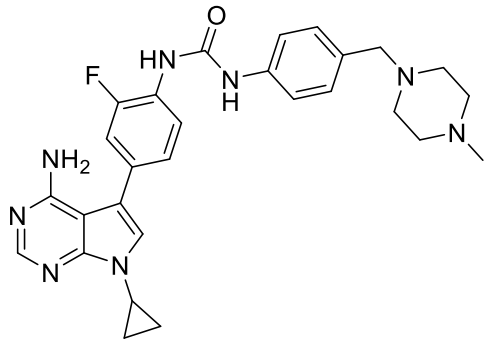
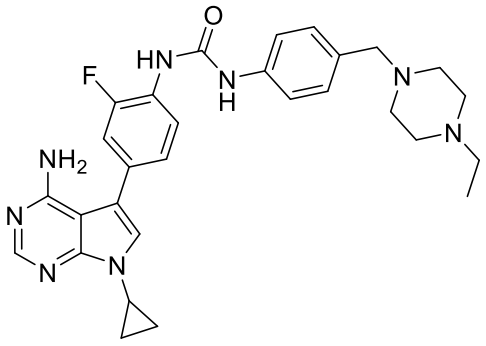

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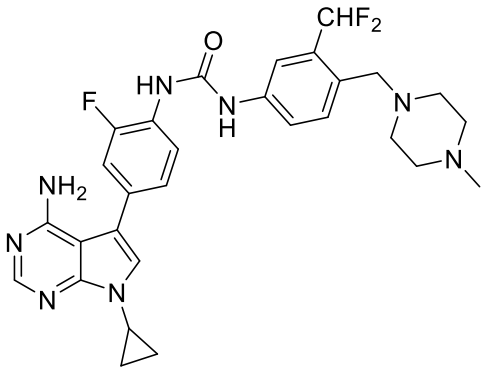
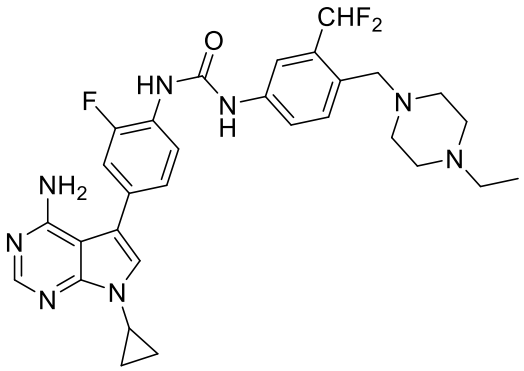
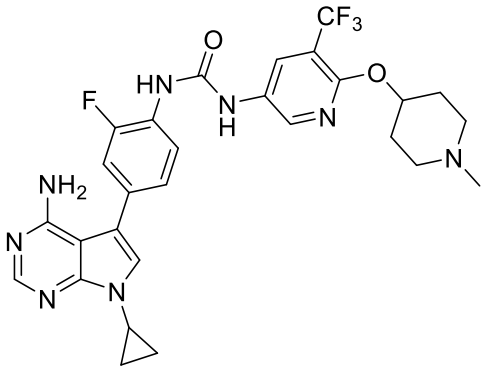
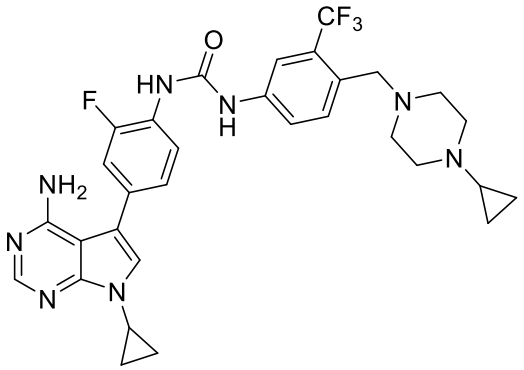
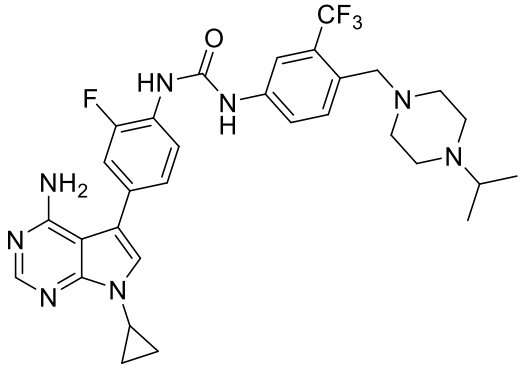
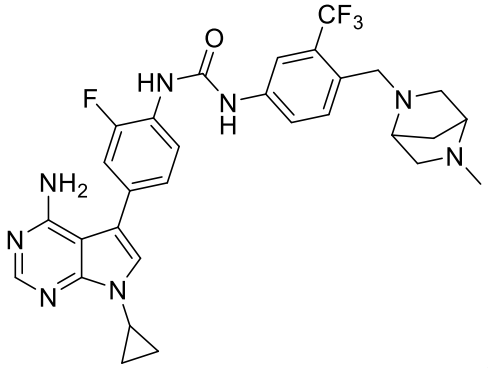
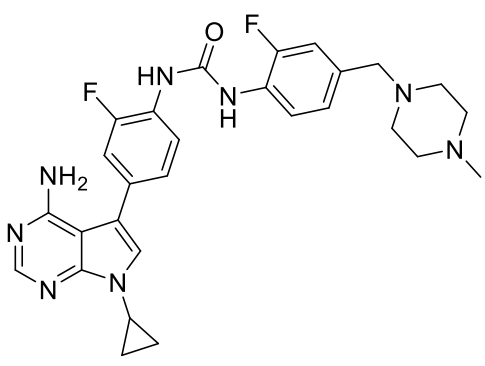
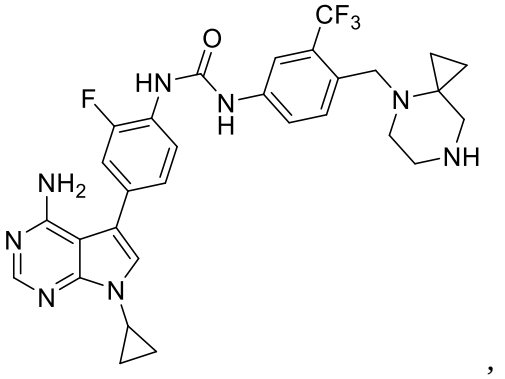

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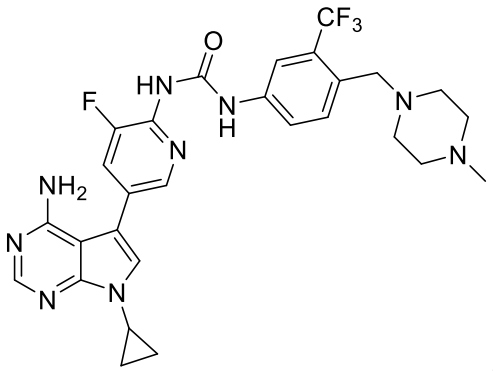
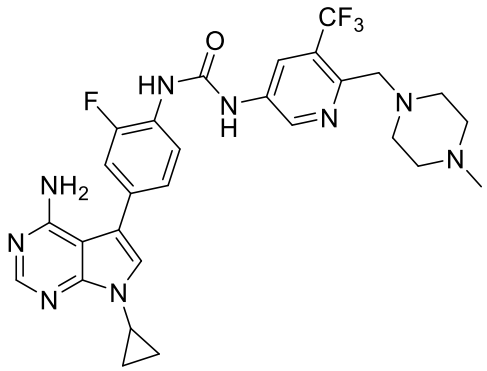
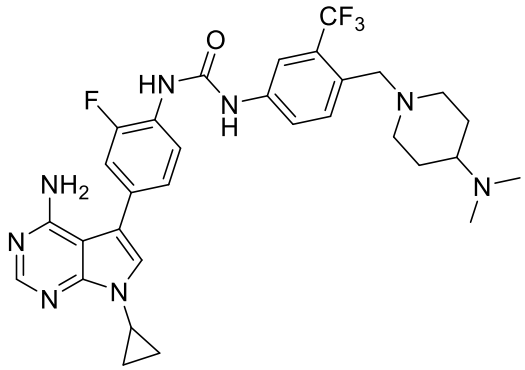
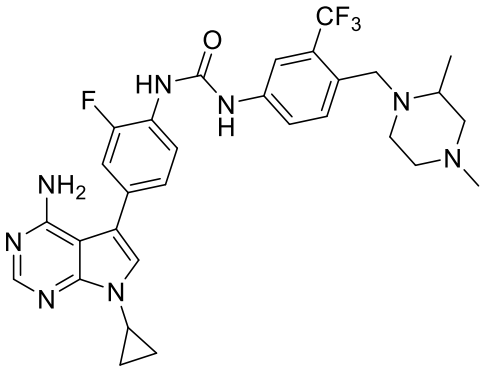
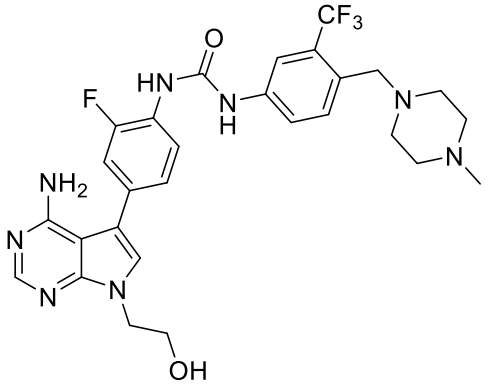
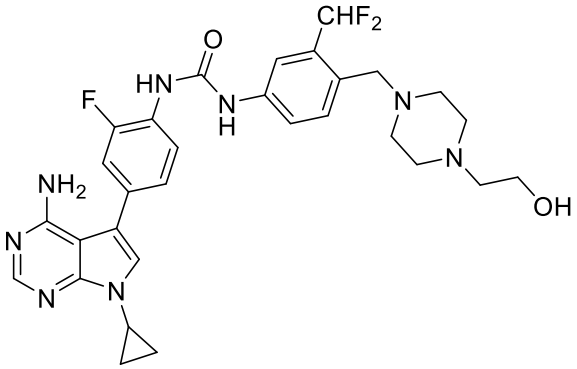
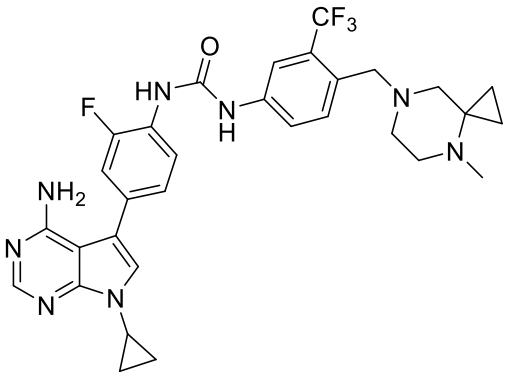
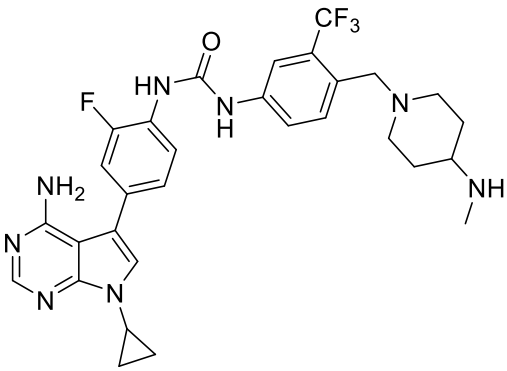

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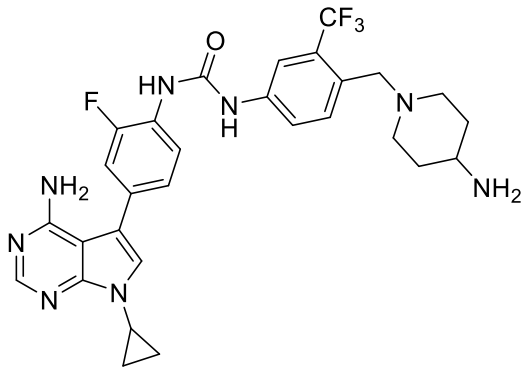
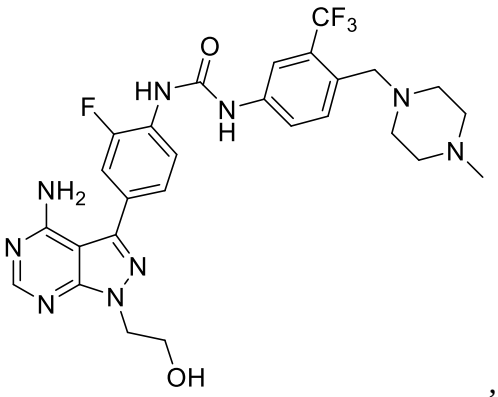
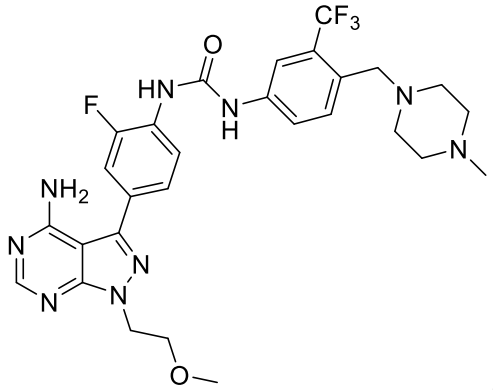
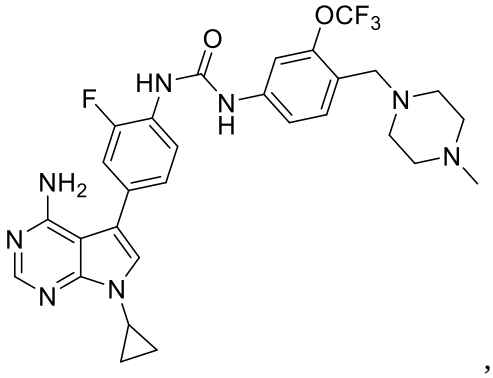
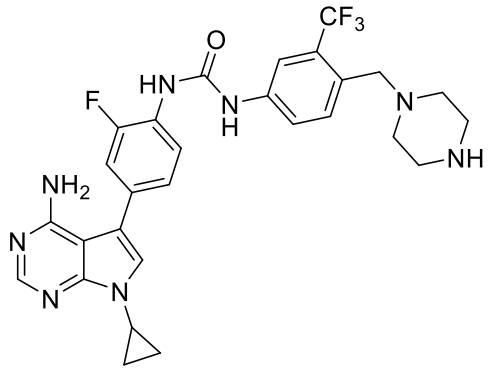
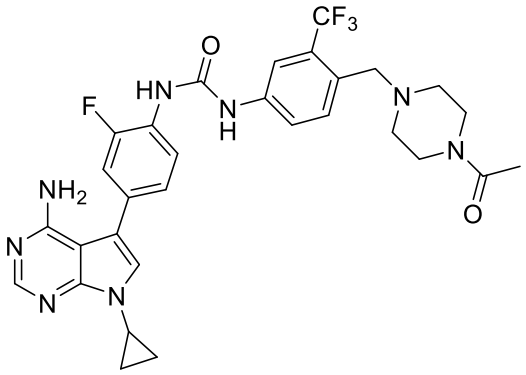
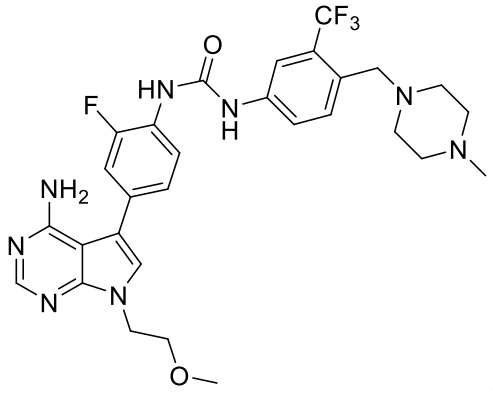
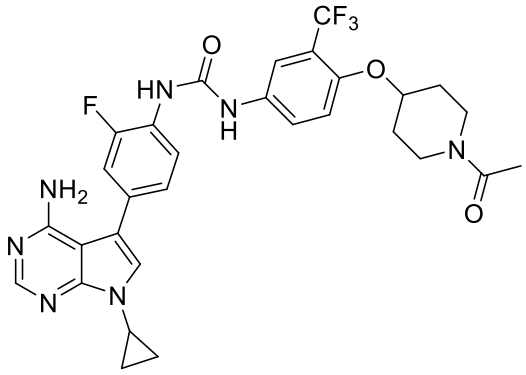

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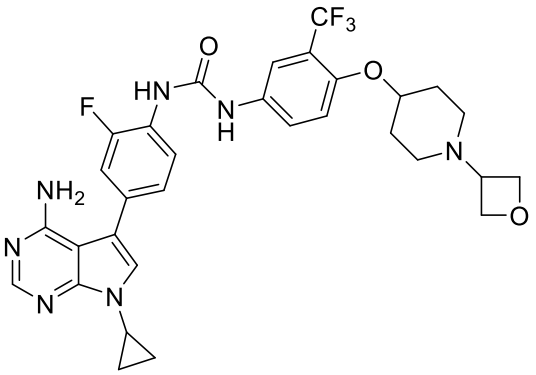
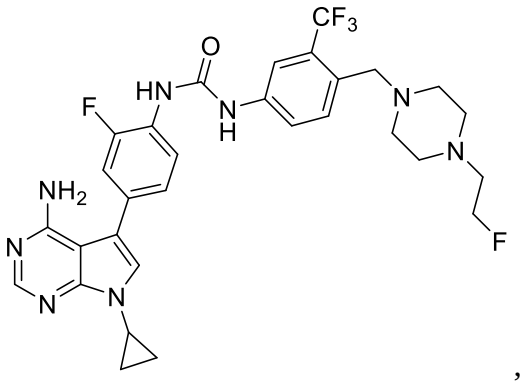
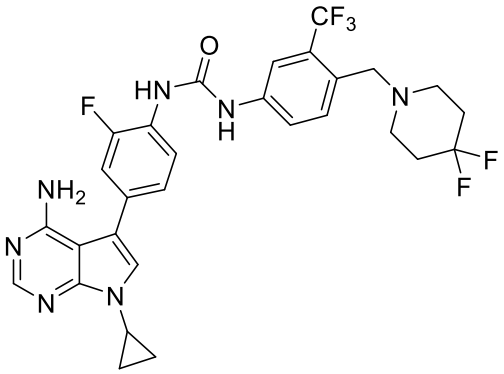
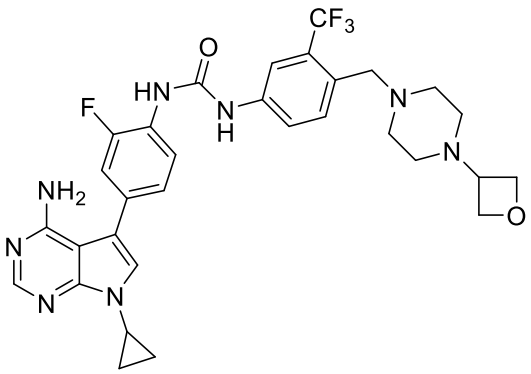
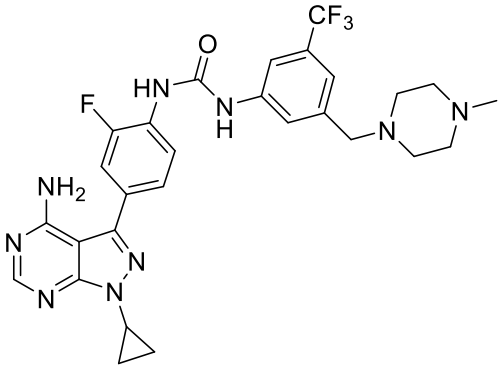
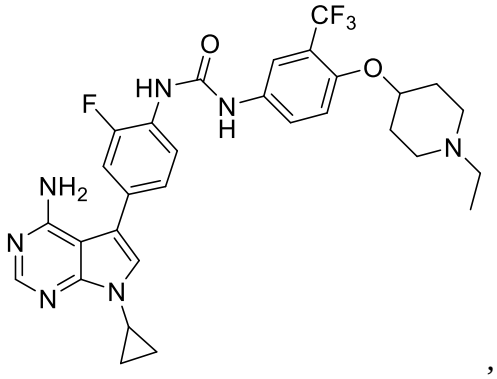
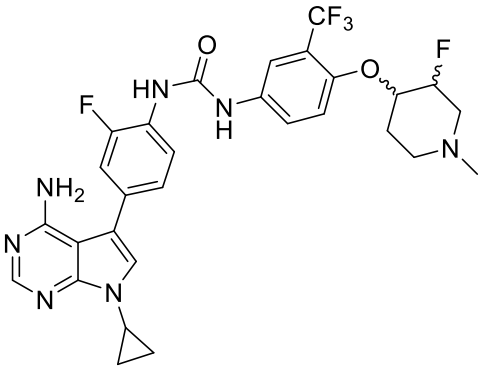
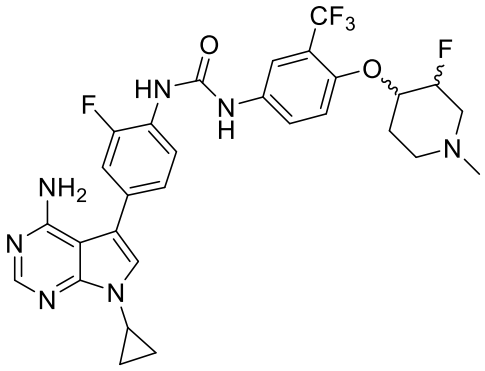

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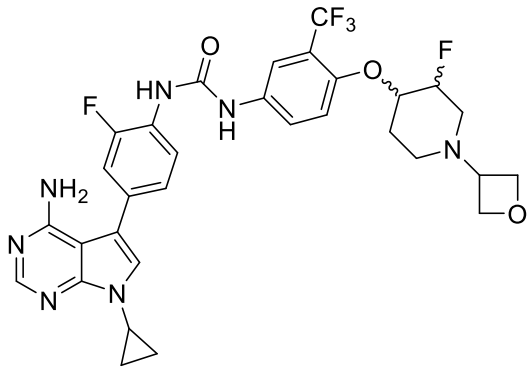
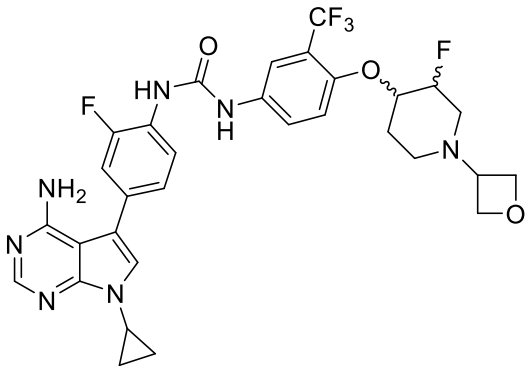
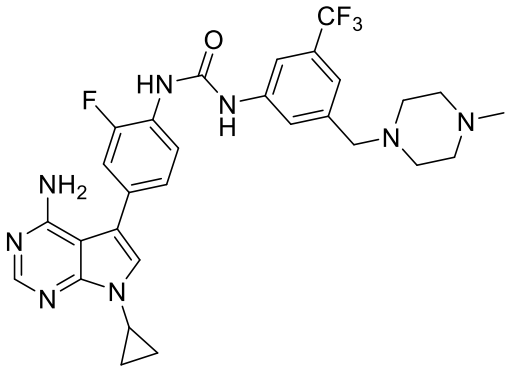
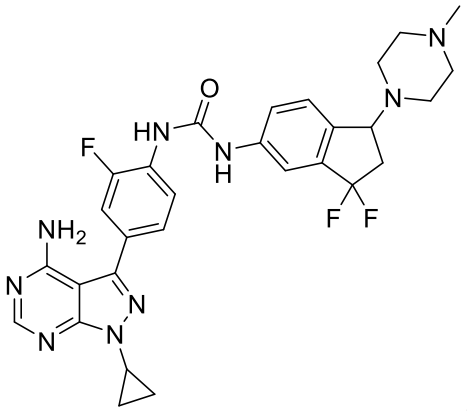
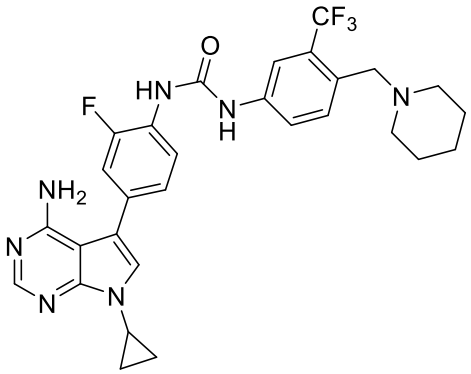
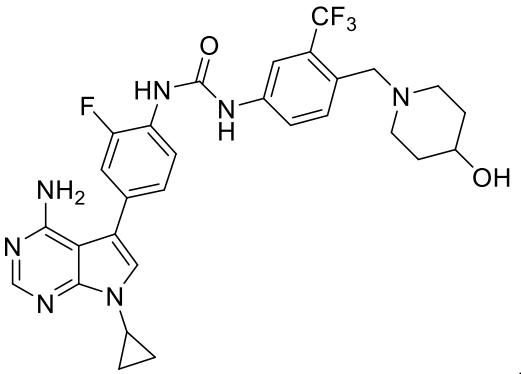
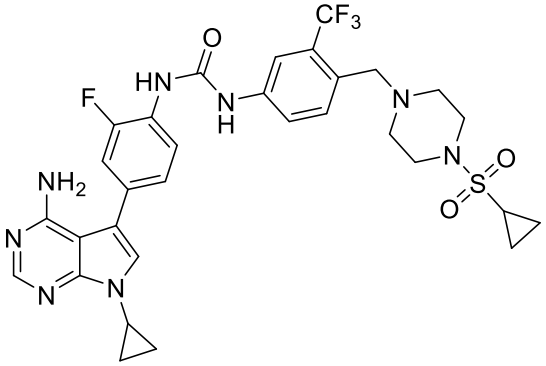
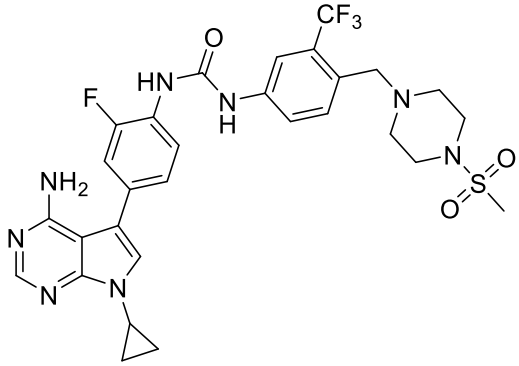

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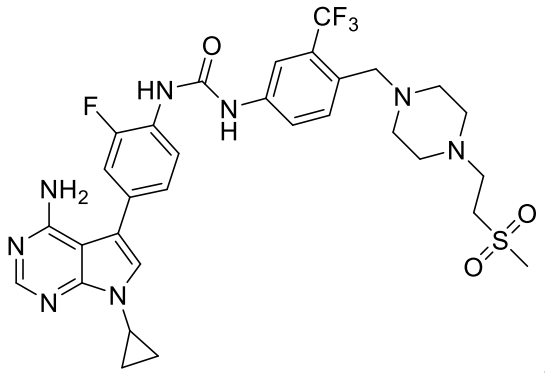
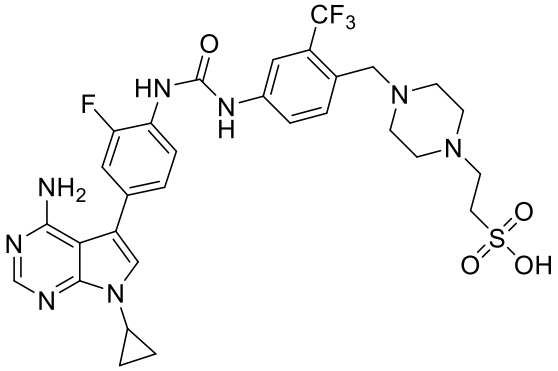
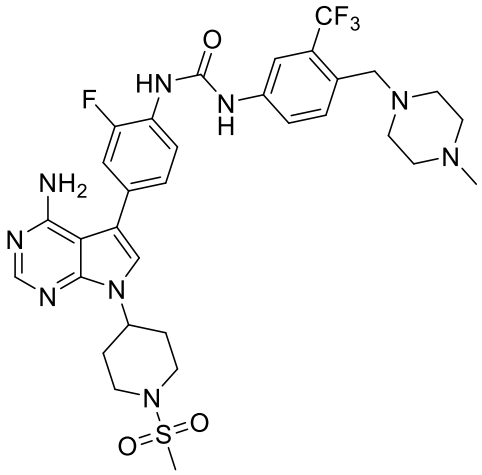
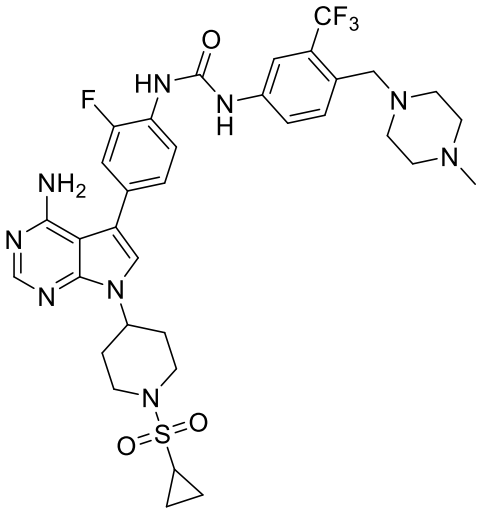
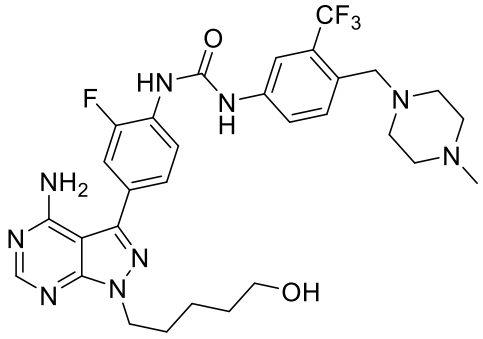

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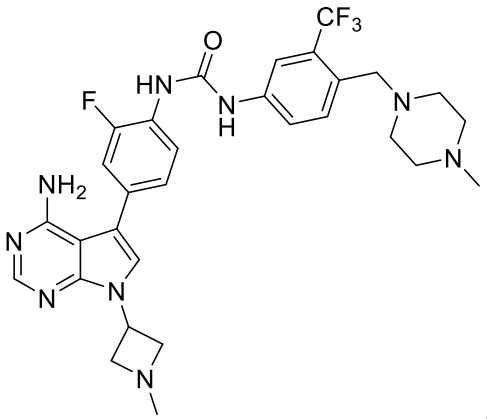
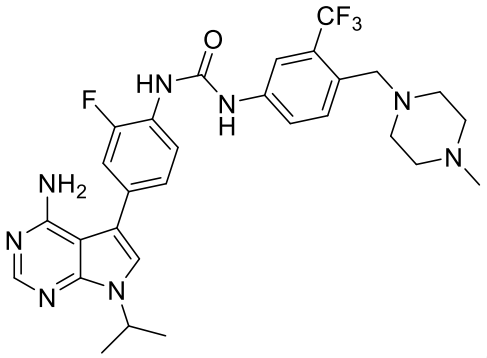
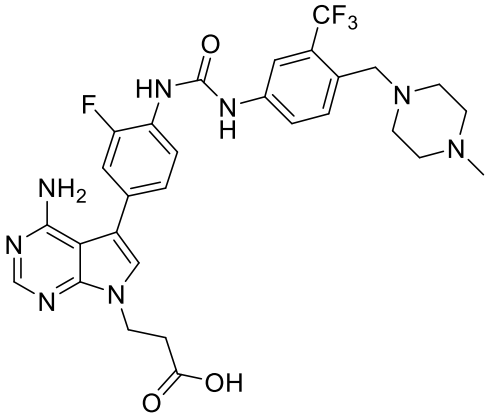
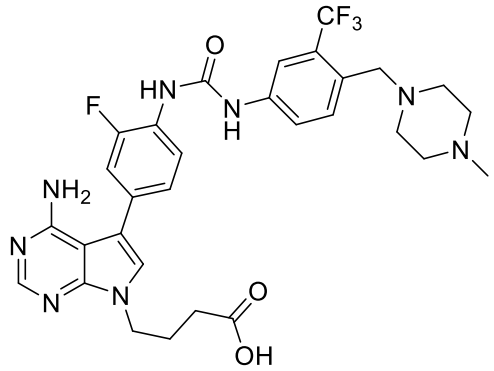
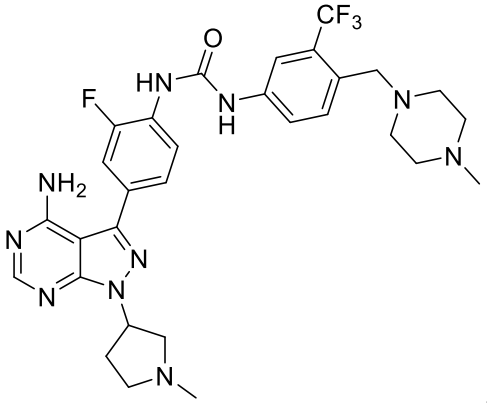
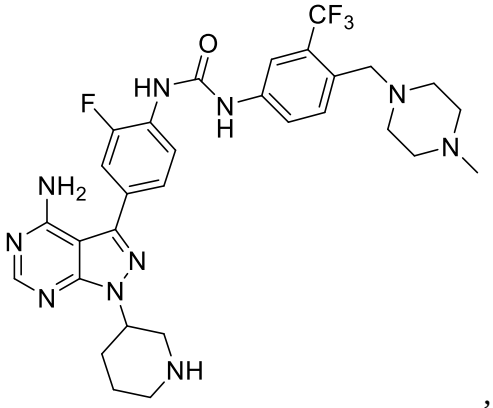
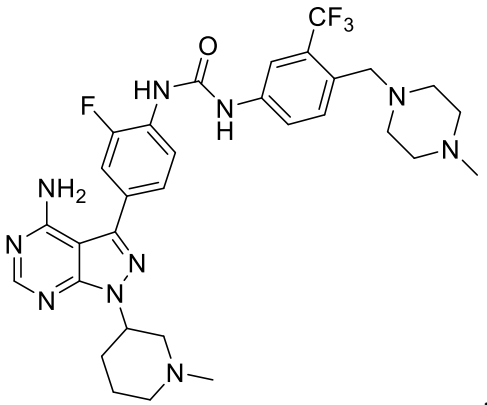
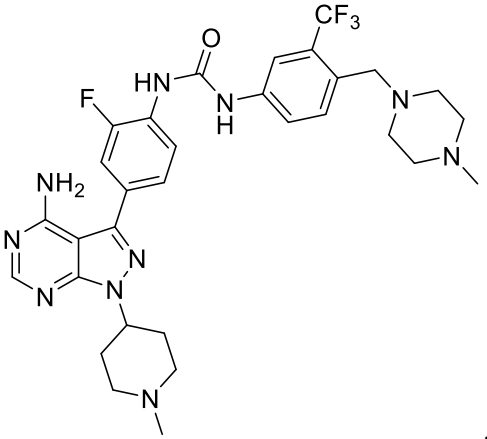

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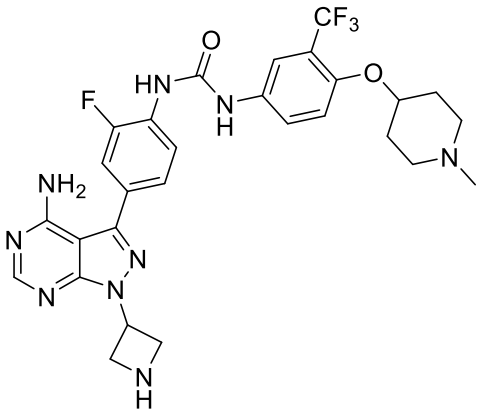
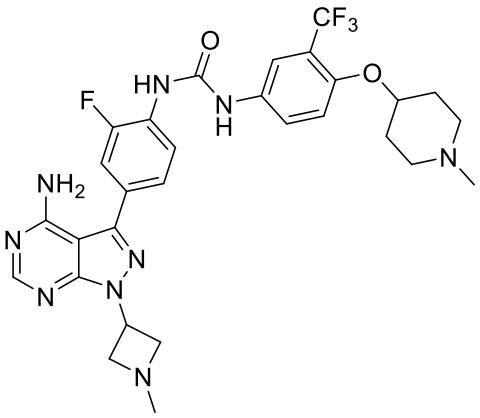
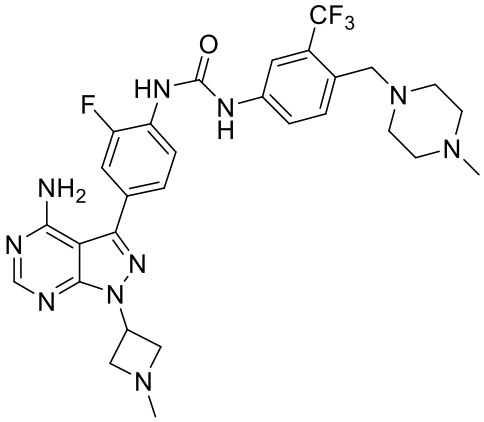
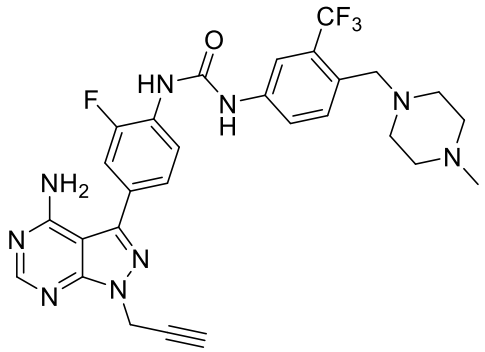
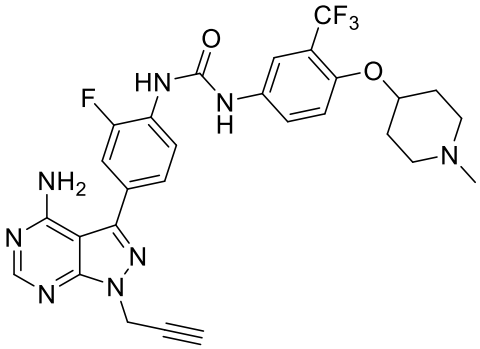
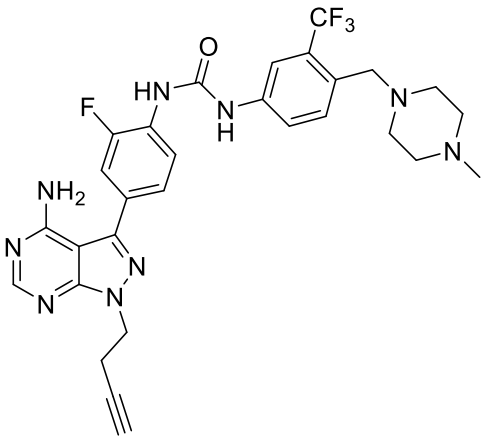

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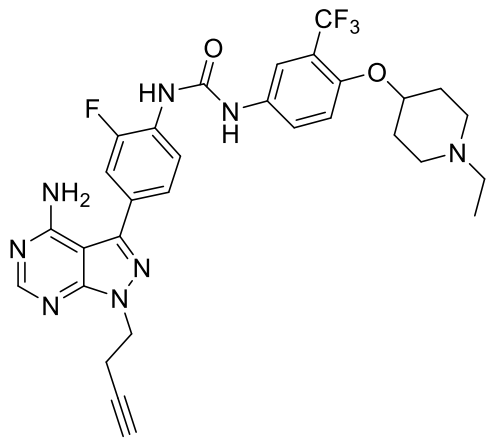

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, or



, or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

21. The compound of any one of claims 1-20, wherein the compound is a modulator of the NLRP3 inflammasome, an inhibitor of NEK7, or both.

22. A pharmaceutical composition comprising the compound of any one of claims 1-21, and a pharmaceutically acceptable carrier, diluent, or excipient.

23. Use of a therapeutically effective amount of a compound of any one of claims 1-21, or the pharmaceutical composition of claim 22 in the manufacture of a medicament for treating a NLRP3-mediated disorder in a subject in need thereof.

24. The use of claim 23, 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, platelet aggregation, cancer, transplantation, sperm motility, erythrocyte deficiency, graft rejection, lung injuries, respiratory diseases, ischemic conditions, and combinations thereof.

25. The method of claim 23 or 24, wherein the disorder is selected from type II diabetes, atherosclerosis, Alzheimer's disease, aging, 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.