

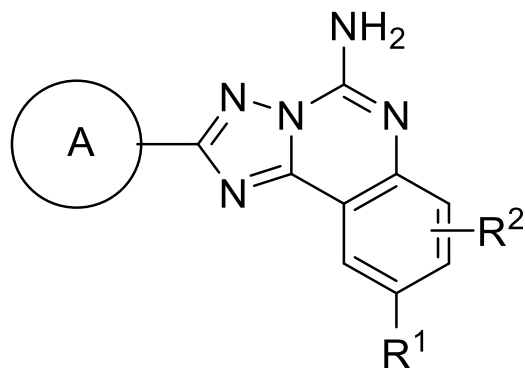
supply to the tumor cells. Furthermore, experiments involving adenylate cyclase activation indicate that A2b receptors are the sole adenosine receptor subtype in certain tumor cells, suggesting that A2b receptor antagonists may exhibit effects on particular tumor types. (See, e.g., Feoktistov, I., et al., (2003) *Circ. Res.* 92:485-492; and P. Fishman, P., et al., *Handb. Exp.*

5 Pharmacol. (2009) 193:399-441).

In view of their promising and varied therapeutic potential, there remains a need in the art for potent and selective inhibitors of the A2a and/or A2b adenosine receptors, for use alone or in combination with other therapeutic agents. The present invention addresses this and other needs.

SUMMARY

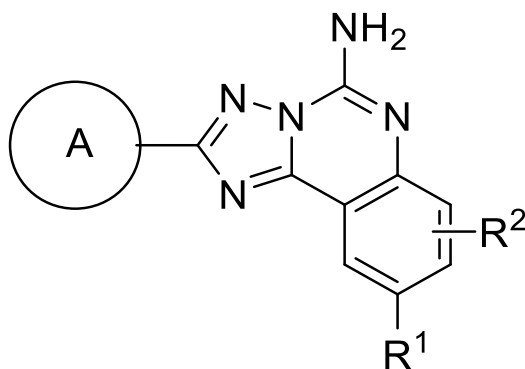
10 The present disclosure provides compounds (hereinafter referred to as compounds of the invention or compounds of the disclosure) which, surprisingly and advantageously, have been found to be inhibitors of the adenosine A2a receptor and/or the adenosine A2b receptor. The compounds of the disclosure have a structure in accordance with the structural Formula (I):



15 (I),

or a pharmaceutically acceptable salt thereof, wherein ring A, R¹, and R² are as defined below.

In one aspect, the present disclosure provides a compound having a structural Formula (I):



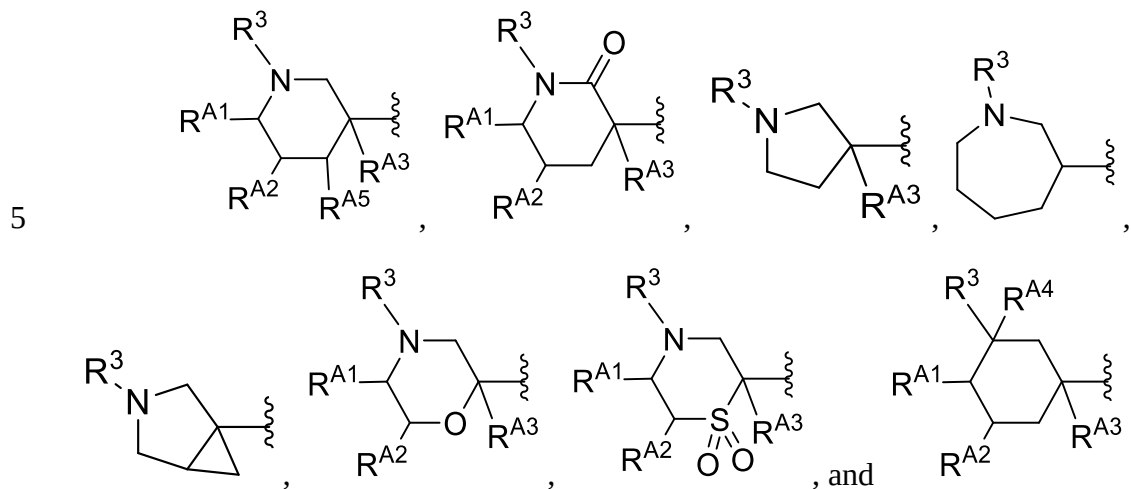
20 (I),

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from F, Cl, (C₁-C₆)alkyl, and O(C₁-C₆)alkyl;

R² is selected from H, F, Cl, (C₁-C₆)alkyl, and O(C₁-C₆)alkyl;

ring A is a moiety selected from:



R³ is selected from pyrazolyl, triazolyl, and pyridinyl, wherein said pyrazolyl and said triazolyl, are substituted with 1 or 2 R^{3A} groups, and wherein said pyridinyl is substituted with 1, 2, or 3 R^{3A} groups, wherein:

10 each R^{3A} is independently selected from (C₁-C₆)alkyl, O(C₁-C₆)alkyl, (C₁-C₆)alkyl-OH, (C₁-C₆)haloalkyl, O(C₁-C₆)haloalkyl, oxo, (C₁-C₄)alkylC(O)(C₁-C₃)alkyl, (C₁-C₄)alkylCH(OH)(C₁-C₃)alkyl, (C₁-C₄)alkylS(O)₂(C₁-C₃)alkyl, -(CH₂)_n(C₃-C₇)cycloalkyl, and -(CH₂)_n4-7 membered monocyclic heterocycloalkyl comprising 1 or 2 ring heteroatoms selected from oxygen and nitrogen, wherein said (C₃-C₇)cycloalkyl, and said 4-7 membered monocyclic heterocycloalkyl are each unsubstituted or substituted with 1, 2, or 3 groups independently selected from F, Cl, OH, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl;

n is 0, 1, or 2;

R^{A1} is selected from H, and (C₁-C₄)alkyl;

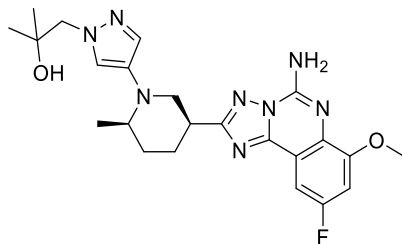
R^{A2} is selected from H, F, and (C₁-C₄)alkyl;

20 R^{A3} is selected from H, F, and (C₁-C₄)alkyl;

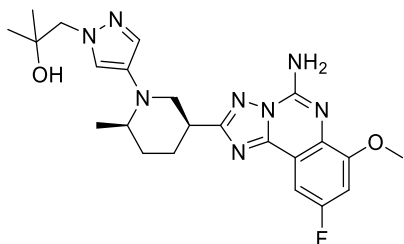
R^{A4} is selected from H and OH; and

R^{A5} is selected from H, F, and (C₁-C₄)alkyl.

In another aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:

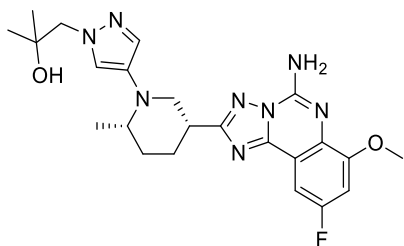


In another aspect, the present disclosure provides a compound, wherein the compound is:

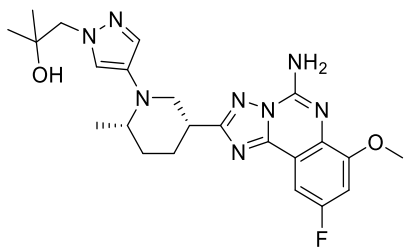


5

In another aspect, the present disclosure provides a compound, or pharmaceutically acceptable salt thereof, wherein the compound is:

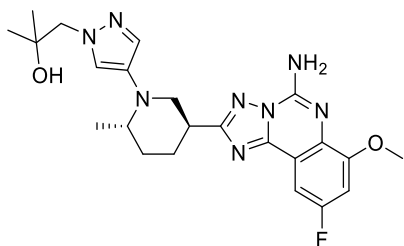


In another aspect, the present disclosure provides a compound, wherein the compound is:

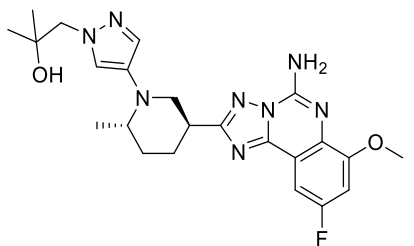


10

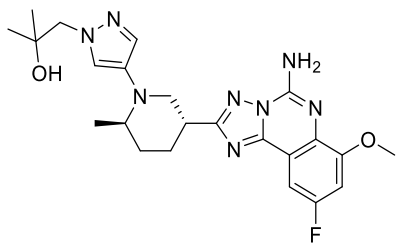
In another aspect, the present disclosure provides a compound, or pharmaceutically acceptable salt thereof, wherein the compound is:



In another aspect, the present disclosure provides a compound, wherein the compound is:

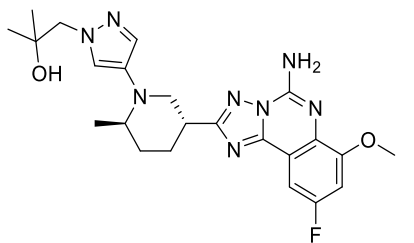


In another aspect, the present disclosure provides a compound, or pharmaceutically acceptable salt thereof, wherein the compound is:

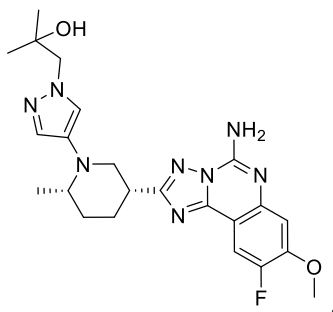


5

In another aspect, the present disclosure provides a compound, wherein the compound is:

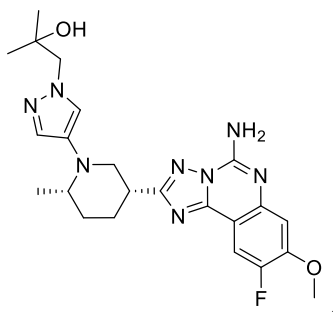


In another aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



10

In another aspect, the present disclosure provides a compound, wherein the compound is:



The present disclosure provides pharmaceutical compositions comprising at least one compound of the disclosure, or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier or diluent. In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Such compositions according to the disclosure may optionally further include one or more additional therapeutic agents as described herein.

The present disclosure provides a method for treating or preventing a disease, condition, or disorder that is mediated, at least in part, by the adenosine A2a receptor and/or the adenosine A2b receptor in a subject (e.g., an animal or human) in need thereof, said method comprising administering to the subject a therapeutically effective amount of at least one compound of the disclosure, or a pharmaceutically acceptable salt thereof, alone or in combination with one or more additional therapeutic agents.

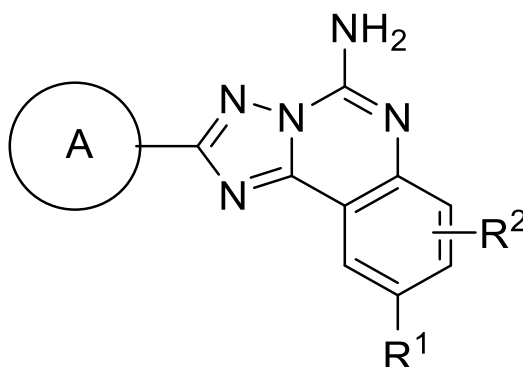
In another aspect, the present disclosure provides use of the compound of the disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

In another aspect, the present disclosure provides the compound of the disclosure, or a pharmaceutically acceptable salt thereof, for use in therapy.

These and other aspects and embodiments of the disclosure are described more fully below.

WHAT IS CLAIMED IS:

1. A compound having a structural Formula (I):



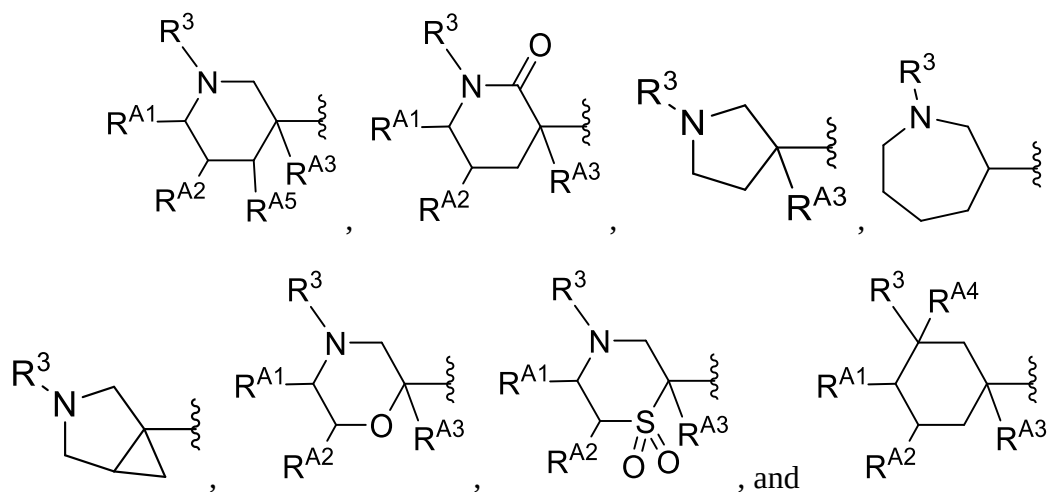
(I),

- 5 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from F, Cl, (C_1-C_6) alkyl, and $O(C_1-C_6)$ alkyl;

R^2 is selected from H, F, Cl, (C_1-C_6) alkyl, and $O(C_1-C_6)$ alkyl;

ring A is a moiety selected from:



- 10 R^3 is selected from pyrazolyl, triazolyl, and pyridinyl, wherein said pyrazolyl and said triazolyl, are substituted with 1 or 2 R^{3A} groups, and wherein said pyridinyl is substituted with 1, 2, or 3 R^{3A} groups, wherein:

- 15 each R^{3A} is independently selected from (C_1-C_6) alkyl, $O(C_1-C_6)$ alkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) haloalkyl, $O(C_1-C_6)$ haloalkyl, oxo, (C_1-C_4) alkylC(O) (C_1-C_3) alkyl, (C_1-C_4) alkylCH(OH) (C_1-C_3) alkyl, (C_1-C_4) alkylS(O) $_2$ (C_1-C_3) alkyl, $-(CH_2)_n(C_3-C_7)$ cycloalkyl, and $-(CH_2)_n$ 4-7 membered monocyclic heterocycloalkyl comprising 1 or 2 ring heteroatoms selected from oxygen and nitrogen, wherein said (C_3-C_7) cycloalkyl, and said 4-7 membered monocyclic heterocycloalkyl are each unsubstituted or substituted with 1, 2, or 3 groups independently
20 selected from F, Cl, OH, (C_1-C_6) alkyl, and (C_1-C_6) haloalkyl;

n is 0, 1, or 2;

R^{A1} is selected from H, and (C₁-C₄)alkyl;

R^{A2} is selected from H, F, and (C₁-C₄)alkyl;

R^{A3} is selected from H, F, and (C₁-C₄)alkyl;

5 R^{A4} is selected from H and OH; and

R^{A5} is selected from H, F, and (C₁-C₄)alkyl.

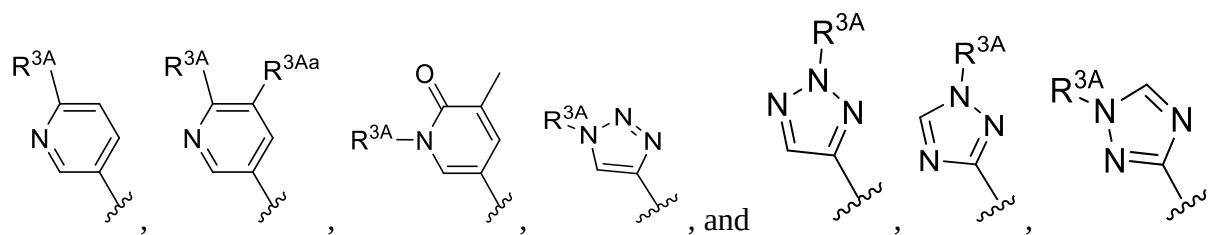
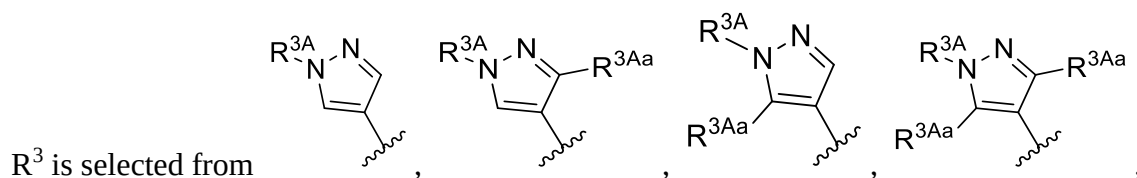
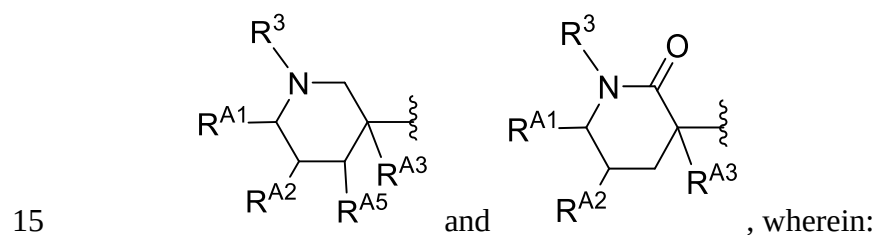
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from F, Cl, and OCH₃; and

10 R^2 is selected from H, F, Cl, CH₃, and OCH₃.

3. The compound of any of claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

ring A is a moiety selected from:

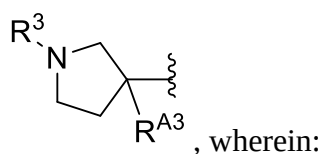
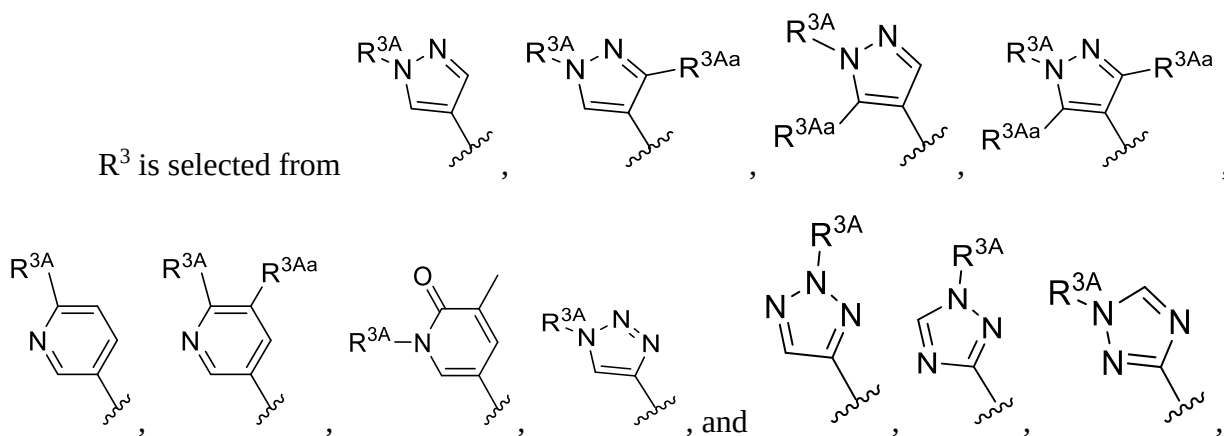


wherein:

each R^{3A} is a moiety selected from:

each R^{3Aa} is independently selected from (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and O(C₁-C₄)haloalkyl.

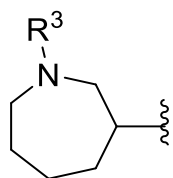
ring A is the moiety:

 R^3 is selected from

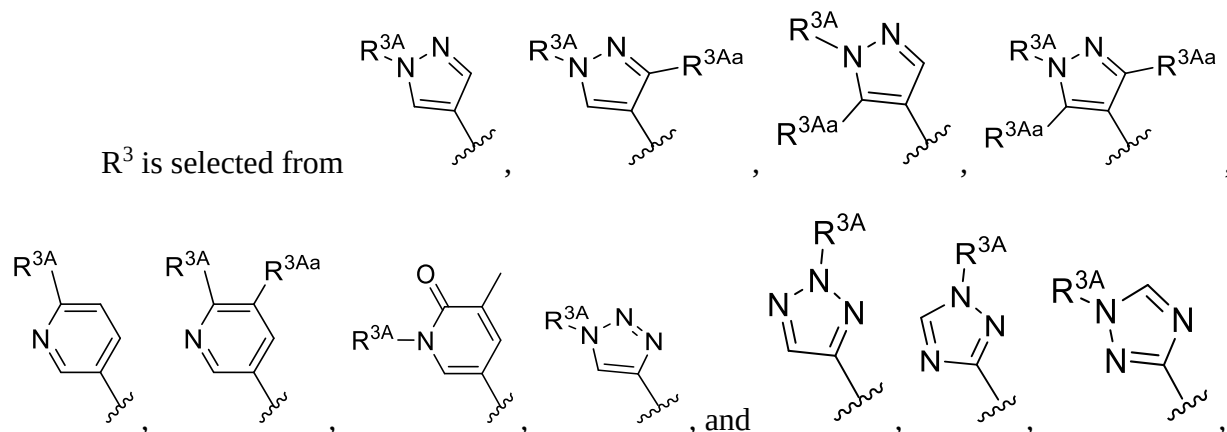
each R^{3A} is a moiety selected from:

each R^{3Aa} is independently selected from (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and O(C₁-C₄)haloalkyl.

ring A is the moiety:



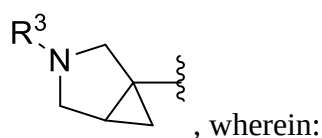
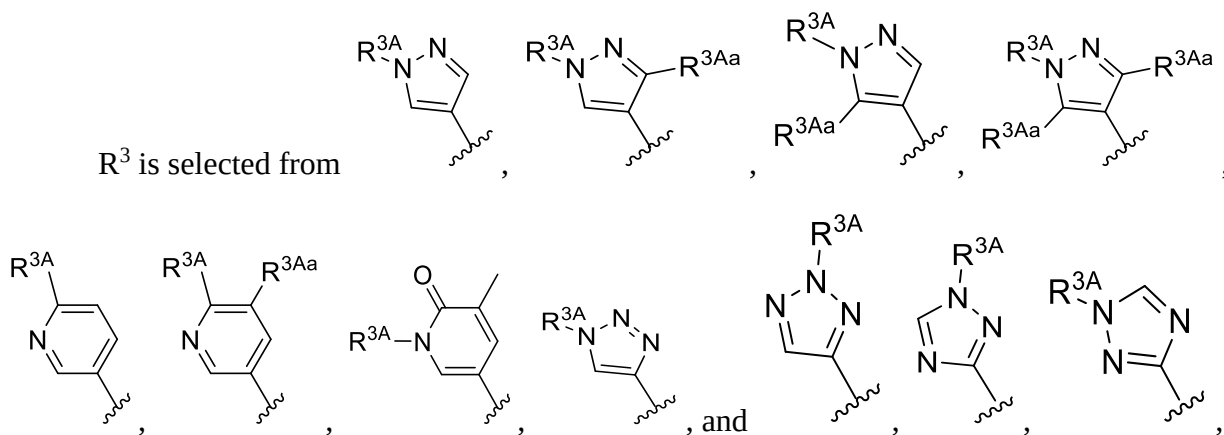
, wherein:



each R^{3A} is a moiety selected from:

each R^{3Aa} is independently selected from (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and O(C₁-C₄)haloalkyl.

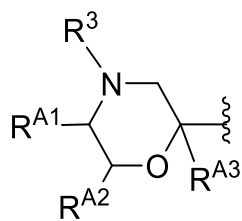
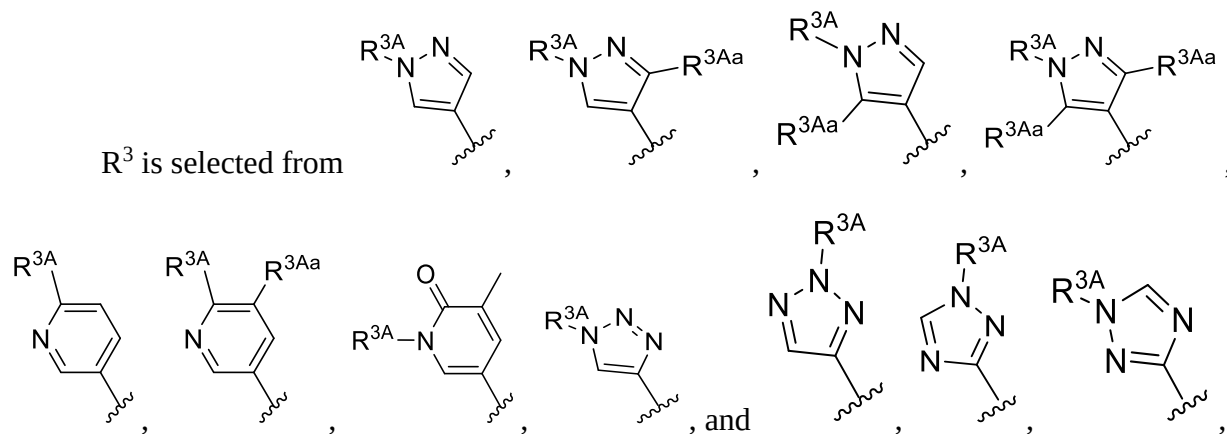
ring A is the moiety:

 R^3 is selected from

each R^{3A} is a moiety selected from:

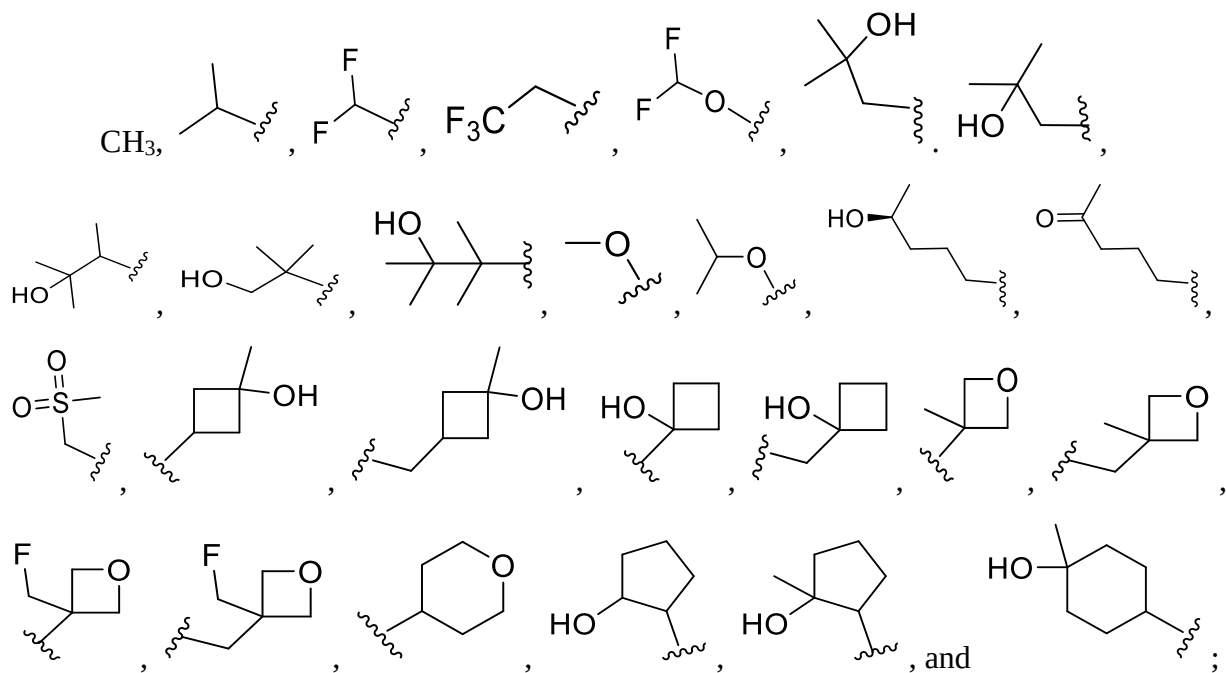
each R^{3Aa} is independently selected from (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and O(C₁-C₄)haloalkyl.

ring A is the moiety:

 R^3 is selected from

15 wherein:

each R^{3A} is a moiety selected from:

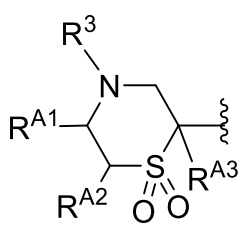


and

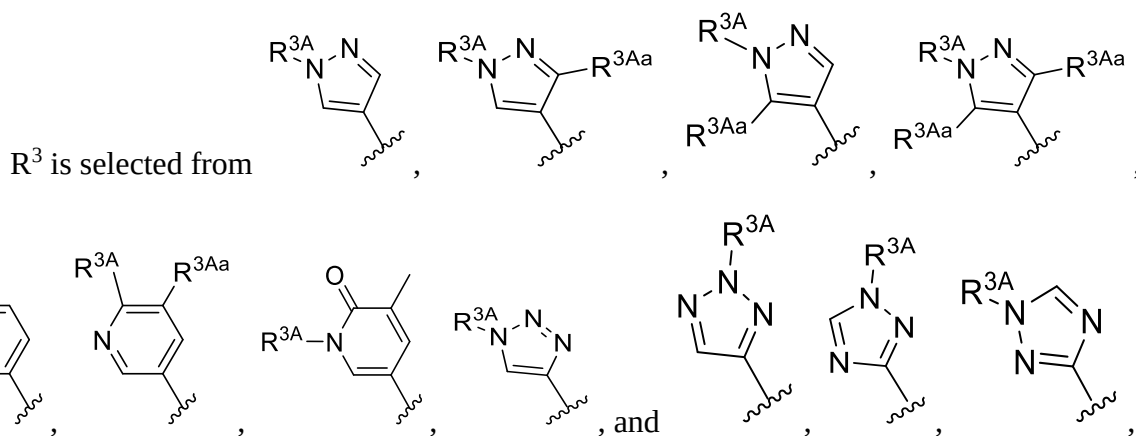
each R^{3Aa} is independently selected from (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and O(C₁-C₄)haloalkyl.

- 10 8. The compound of any of claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

ring A is the moiety:

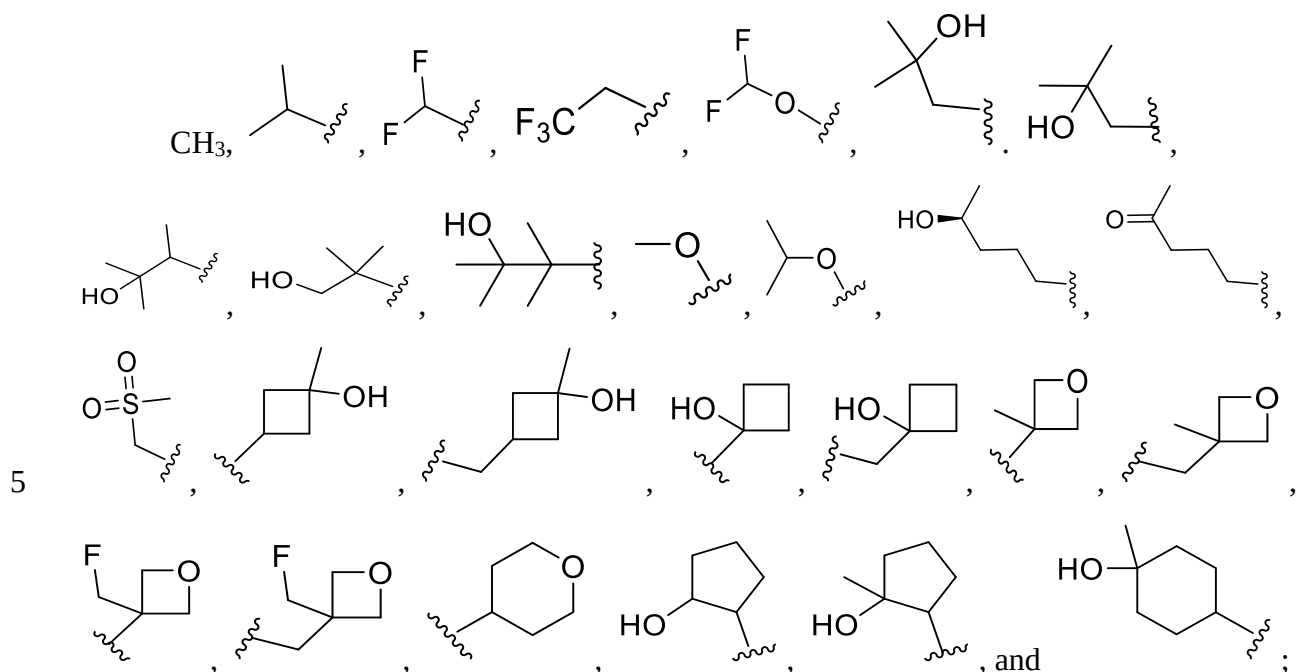


, wherein:



wherein:

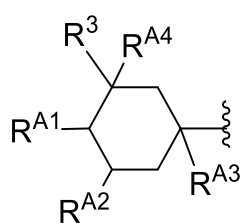
each R^{3A} is a moiety selected from:



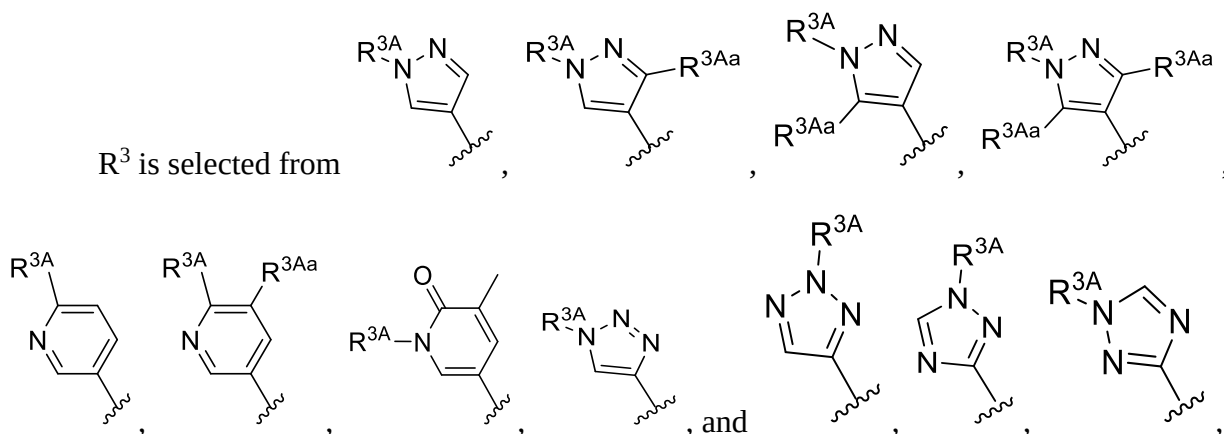
and each R^{3Aa} is independently selected from (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and O(C₁-C₄)haloalkyl.

10 9. The compound of any of claims 1 or 2, or a pharmaceutically acceptable salt thereof,
wherein:

ring A is the moiety:



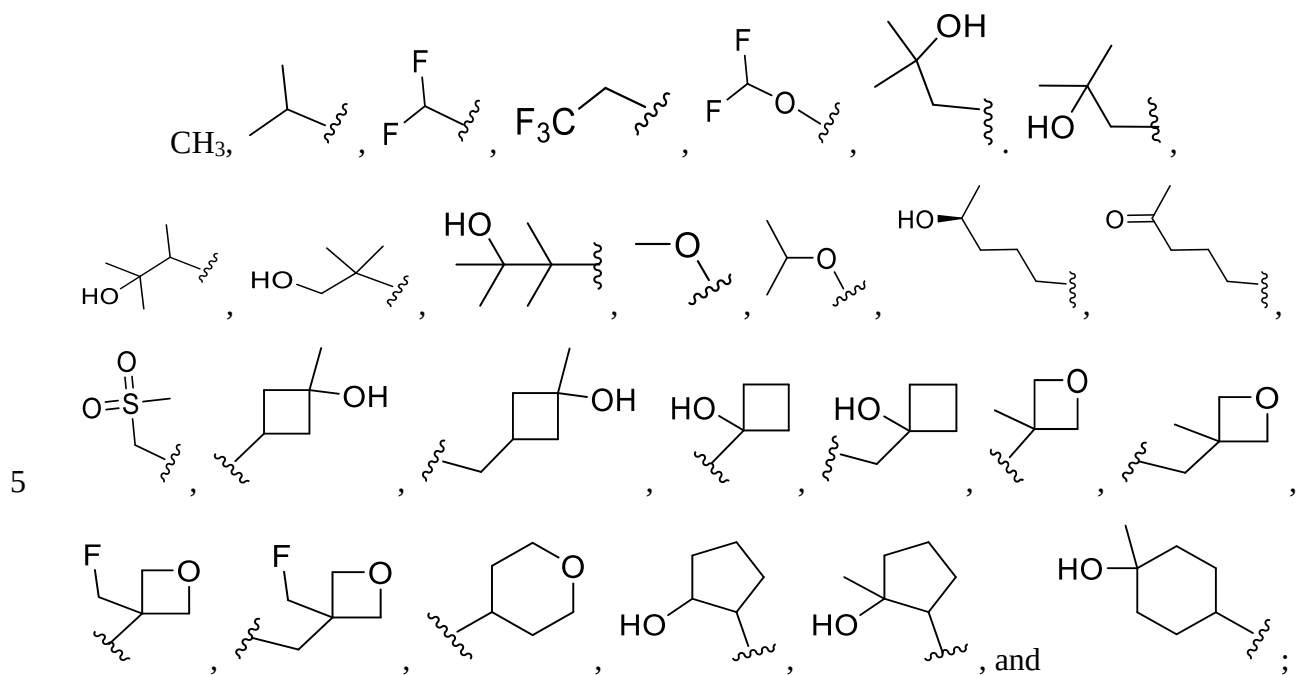
, wherein:



15

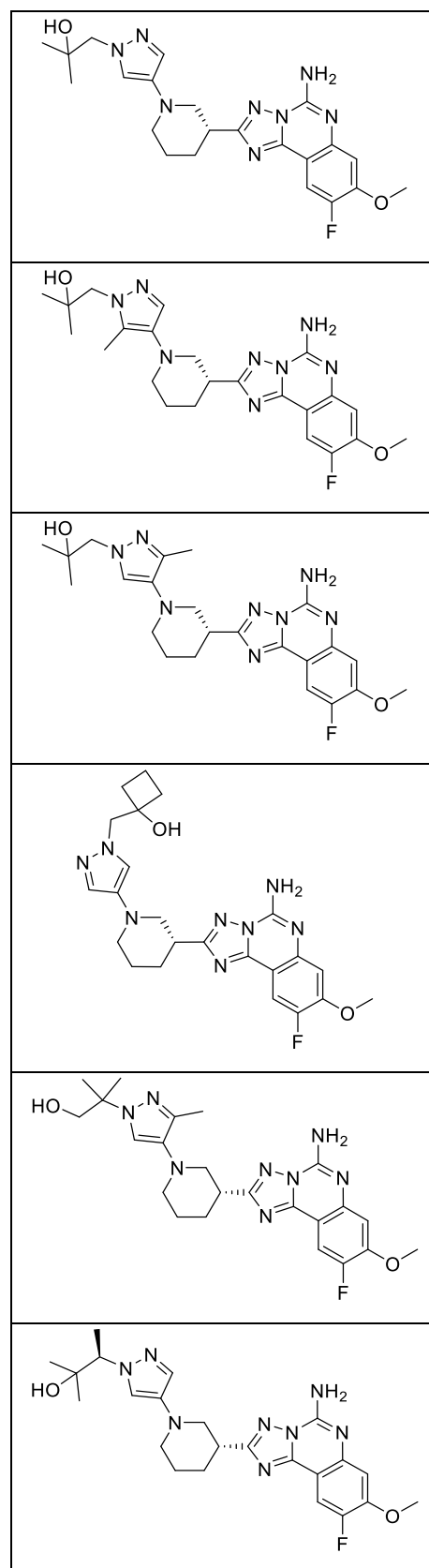
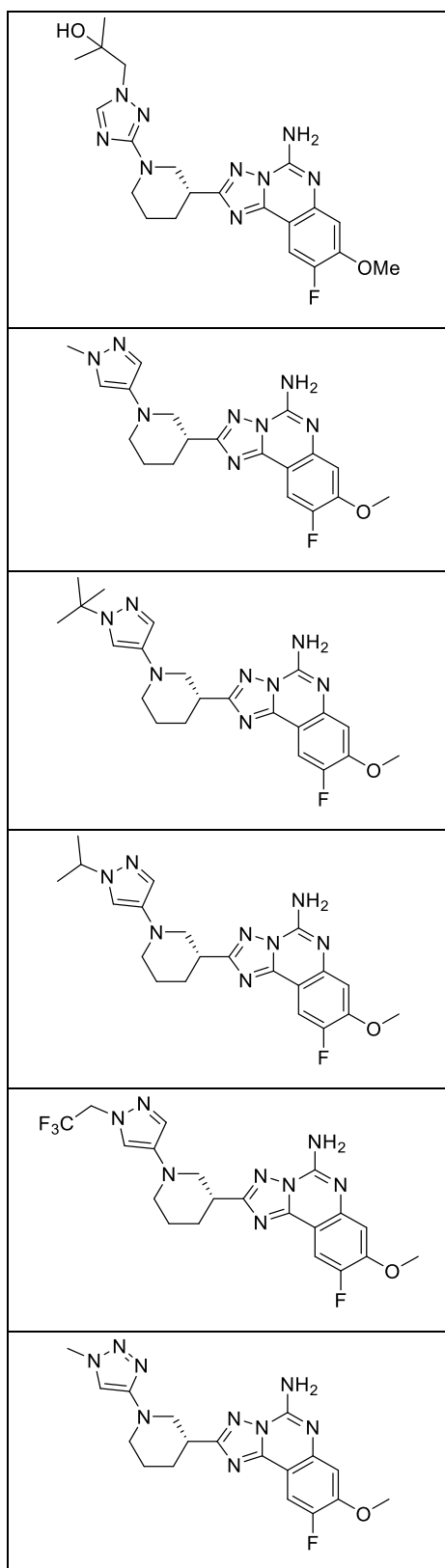
wherein:

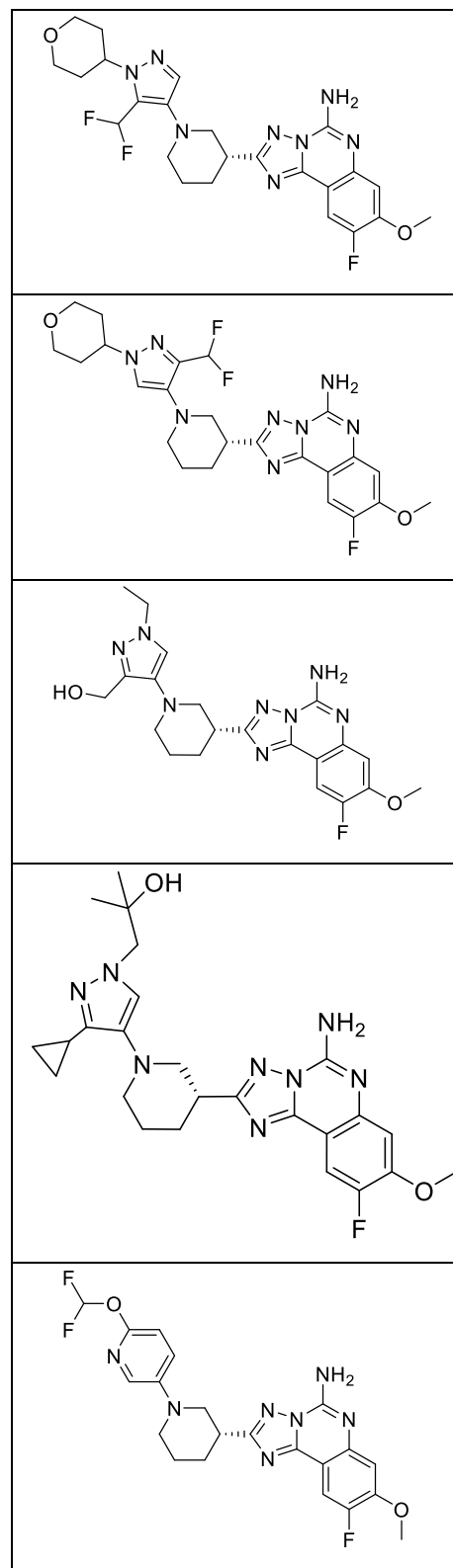
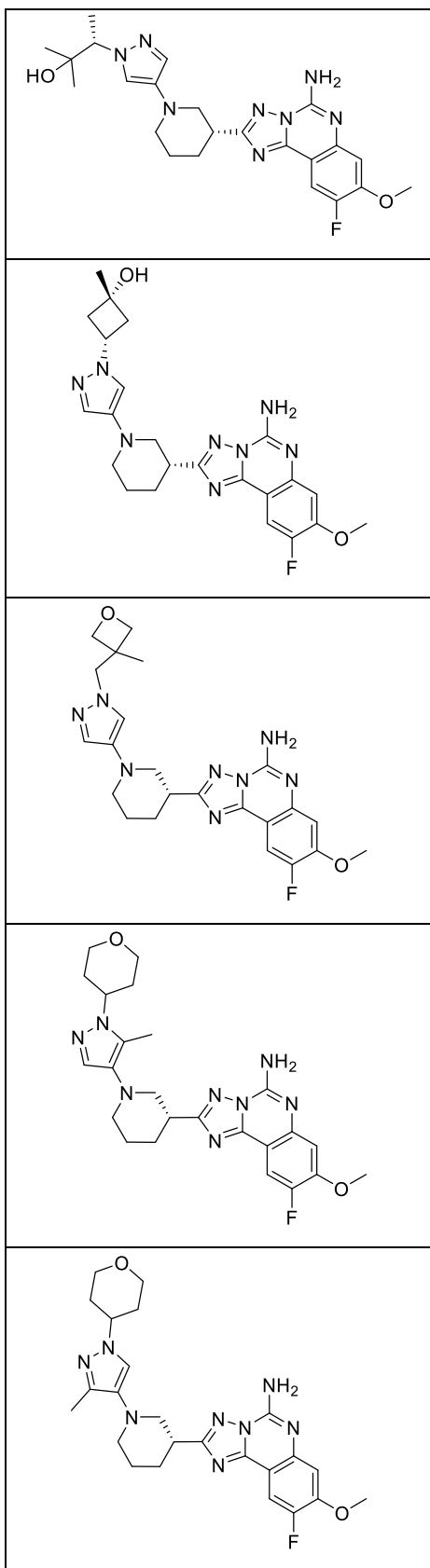
each R^{3A} is a moiety selected from:

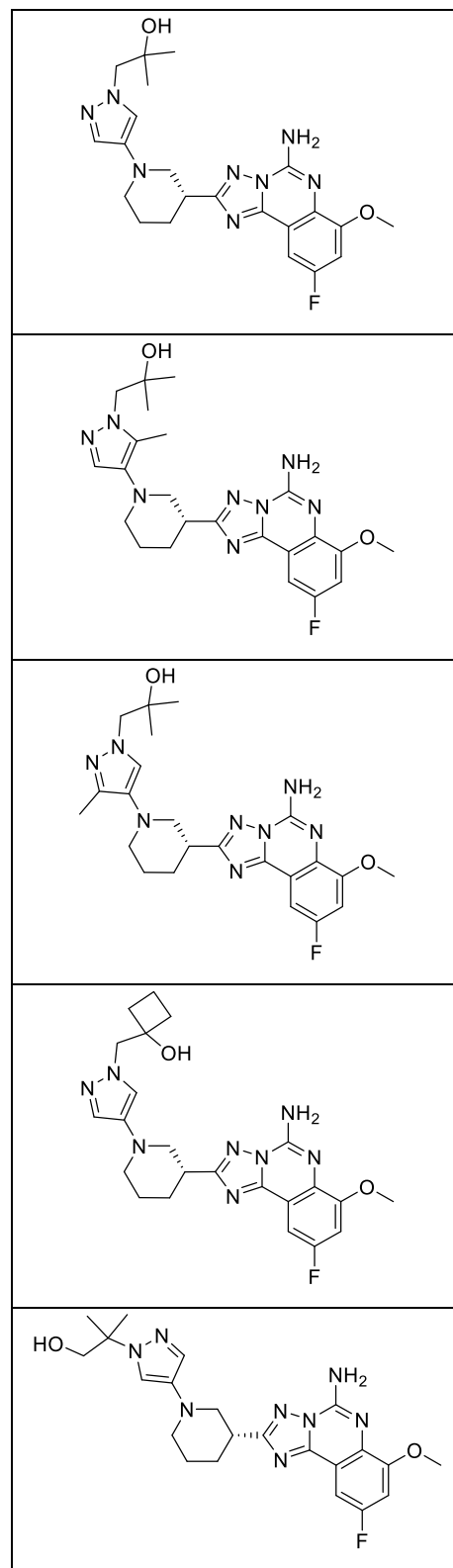
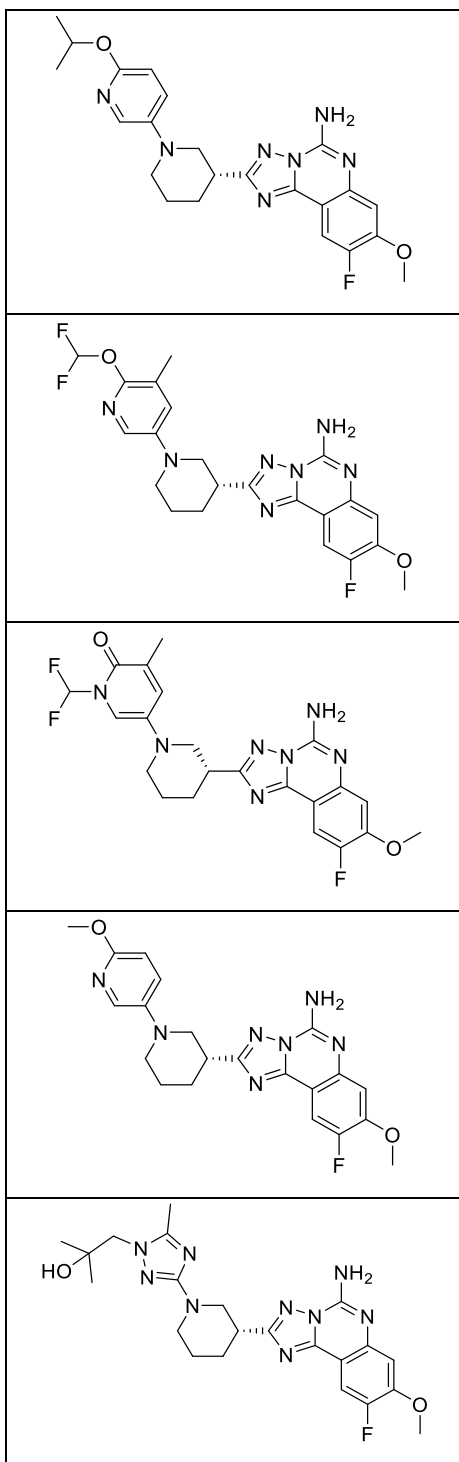


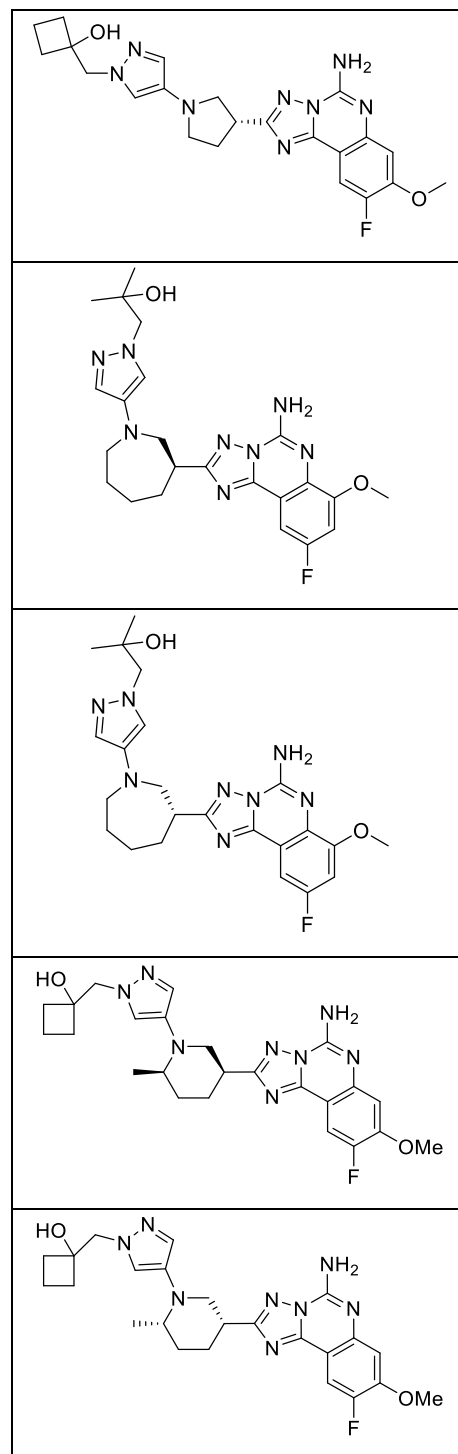
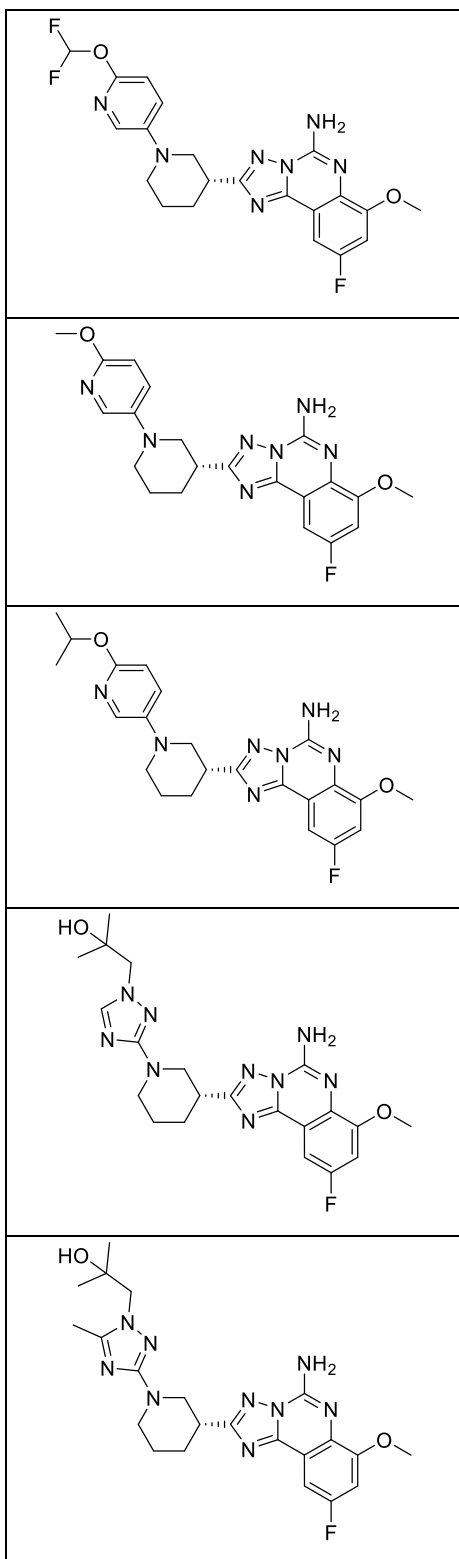
each R^{Aa} is independently selected from (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and O(C₁-C₄)haloalkyl;

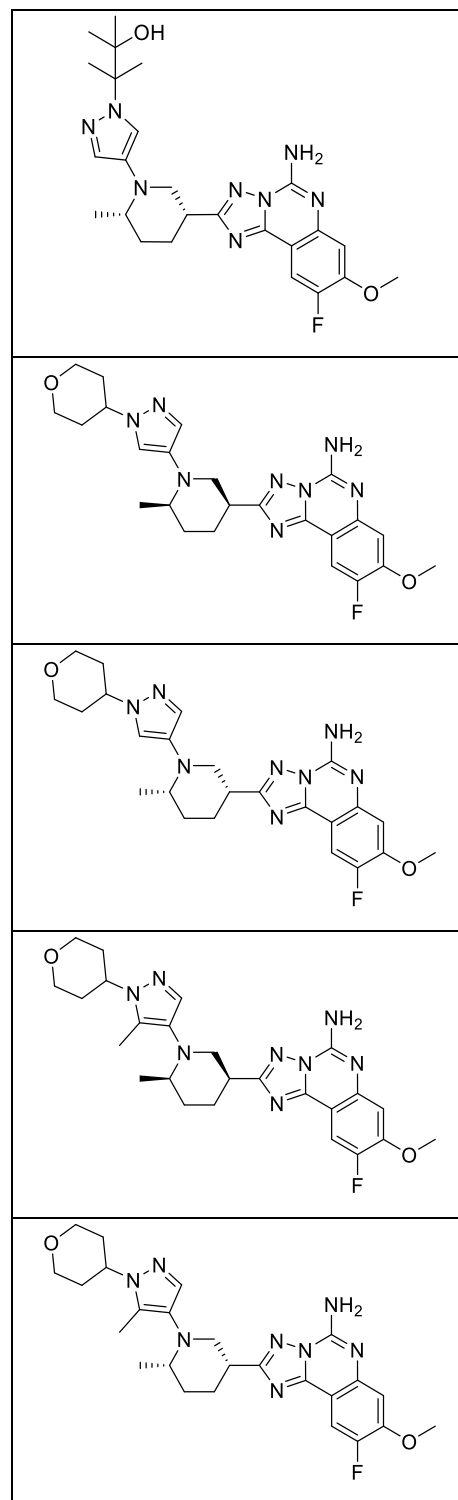
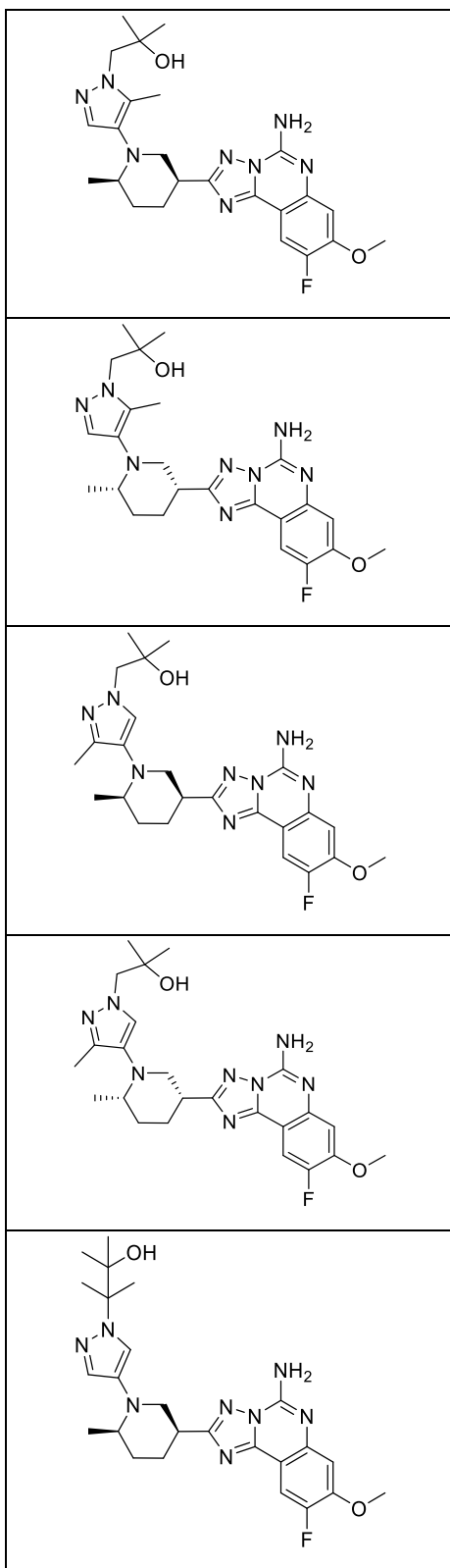
- 10 10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from:

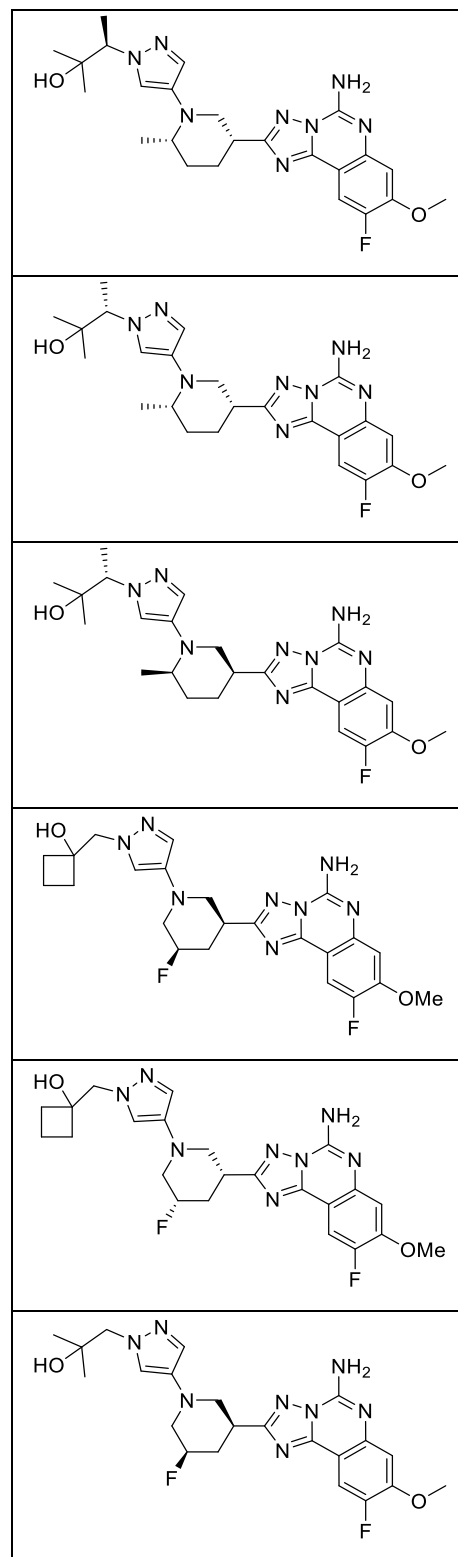
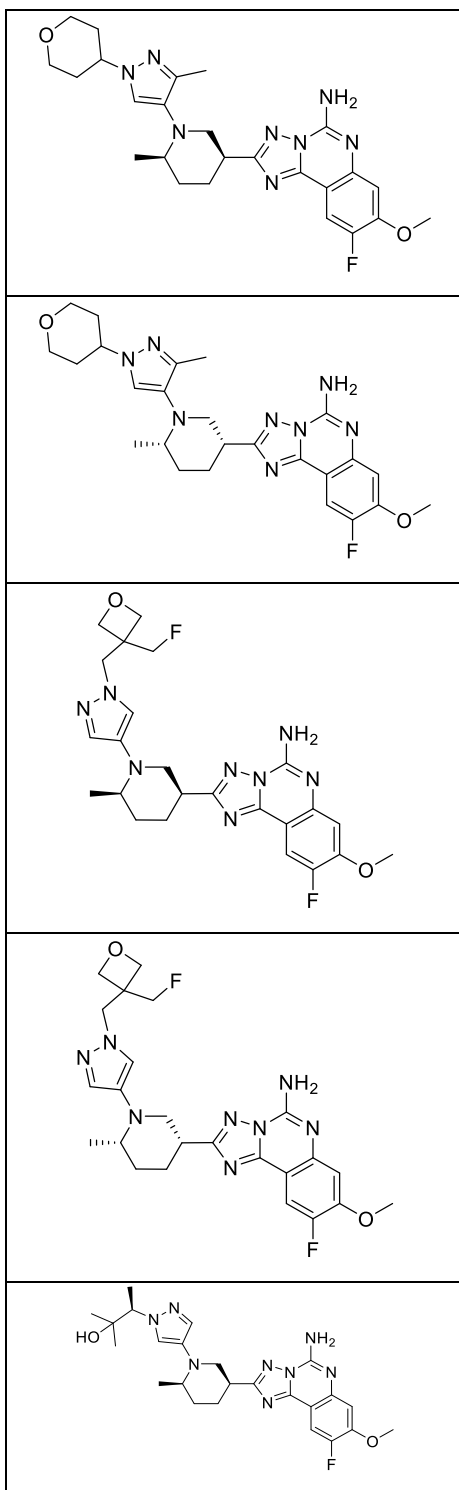


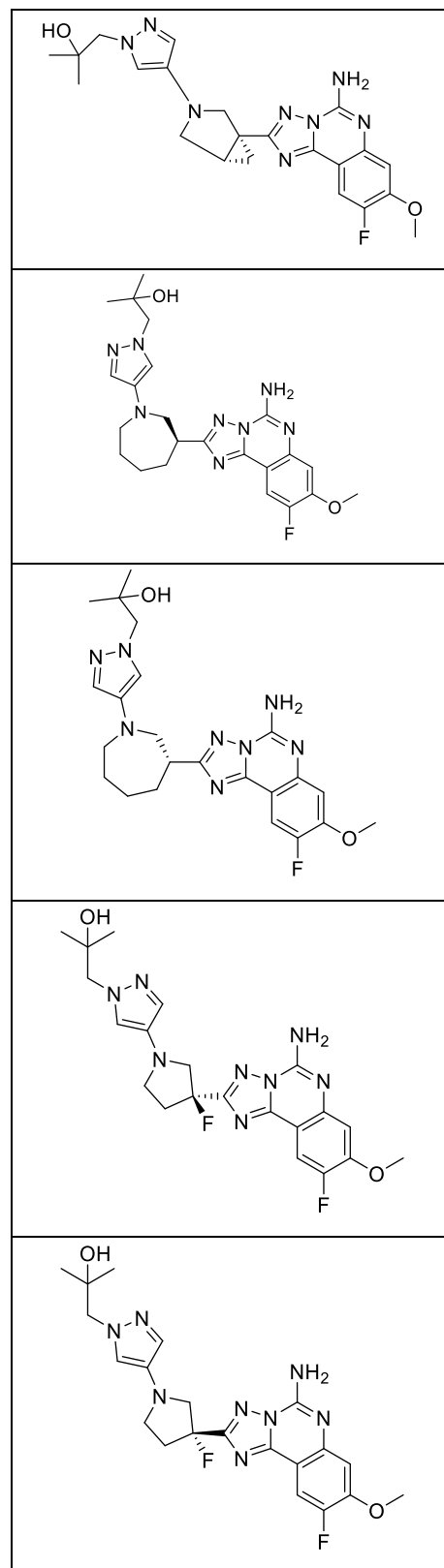
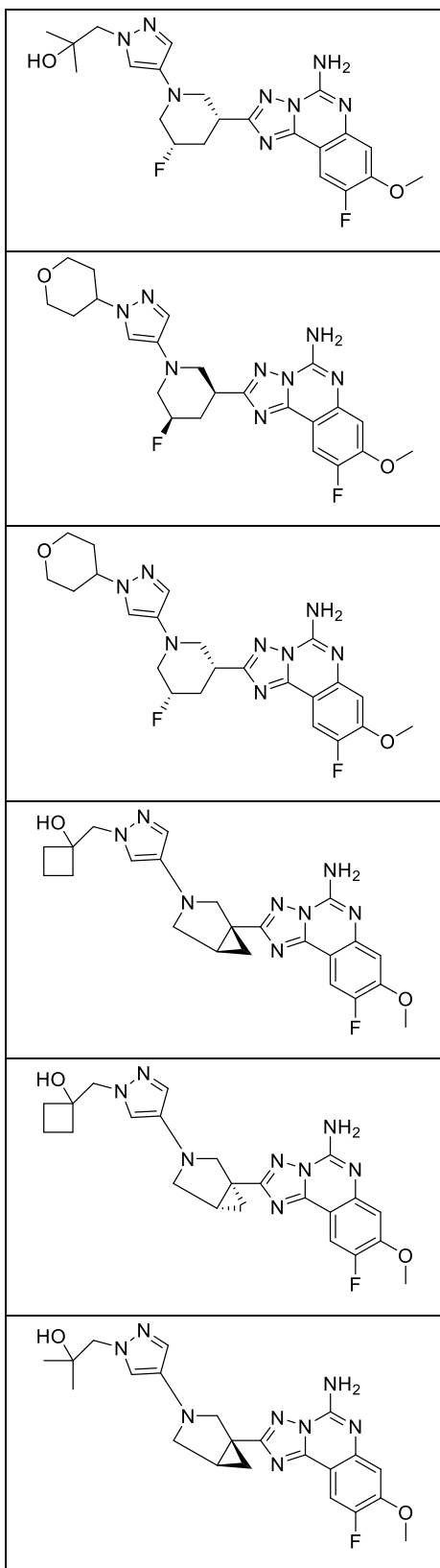


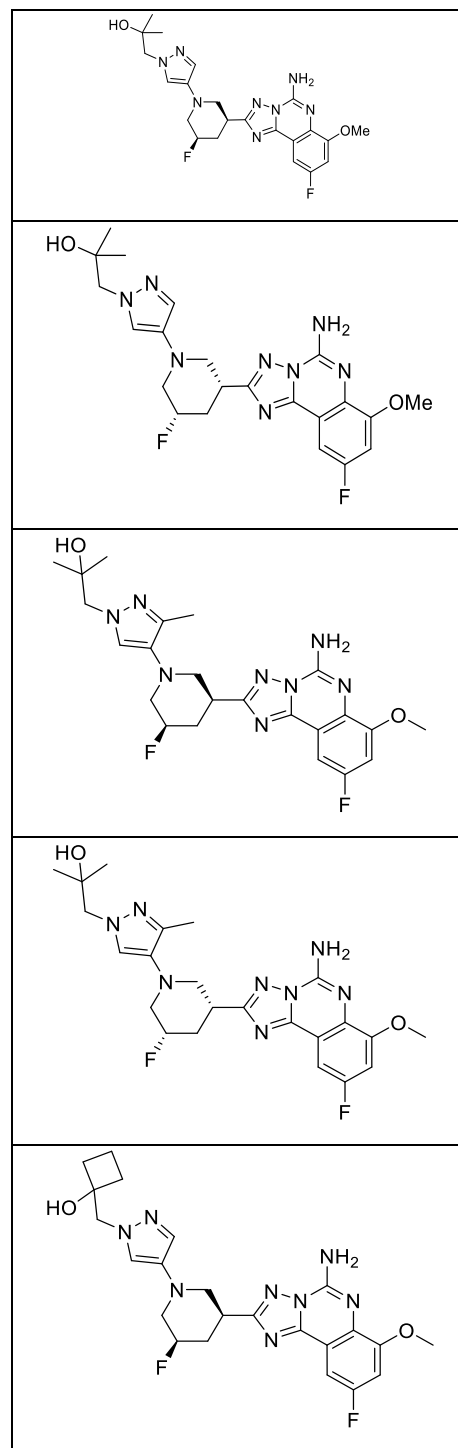
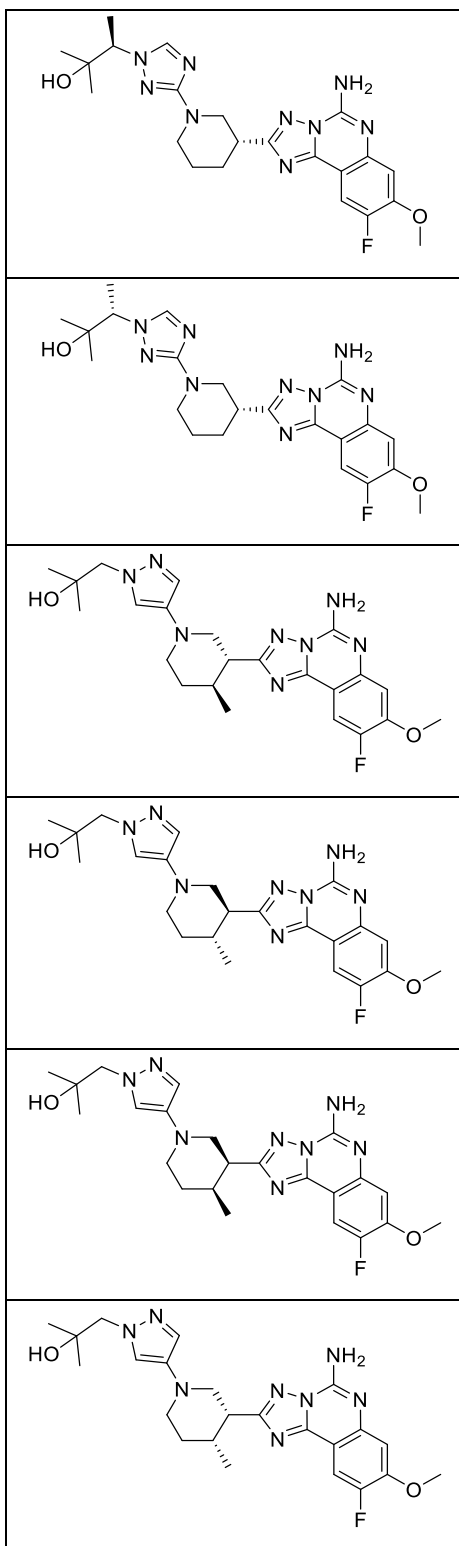


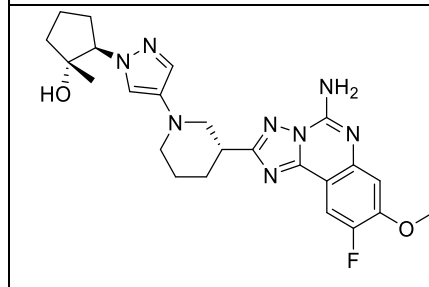
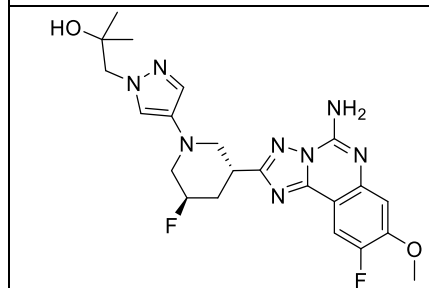
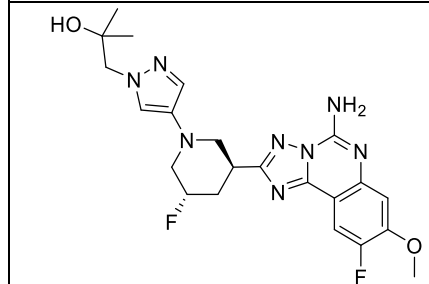
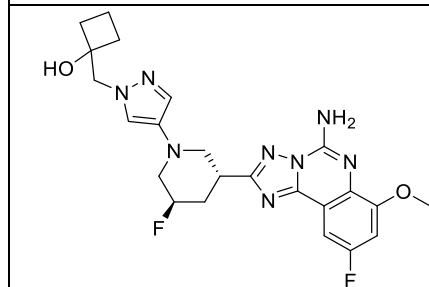
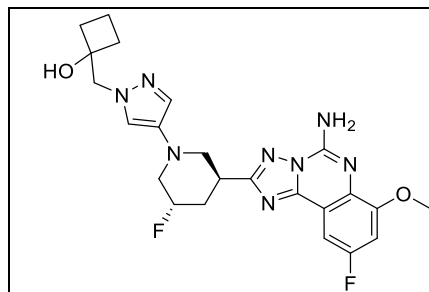
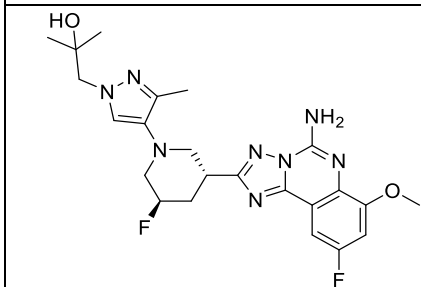
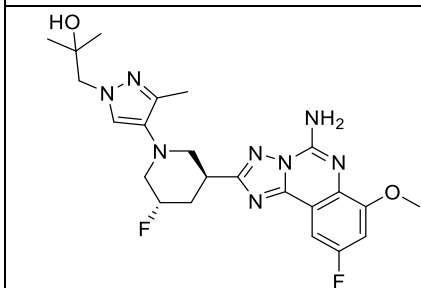
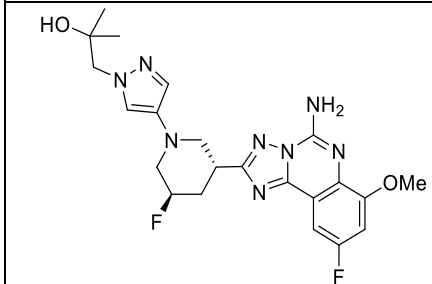
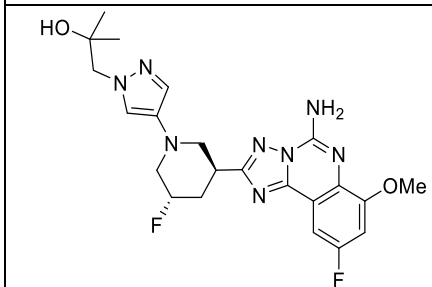
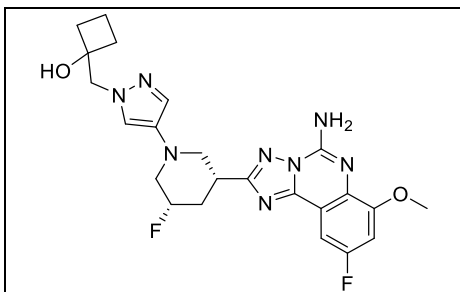


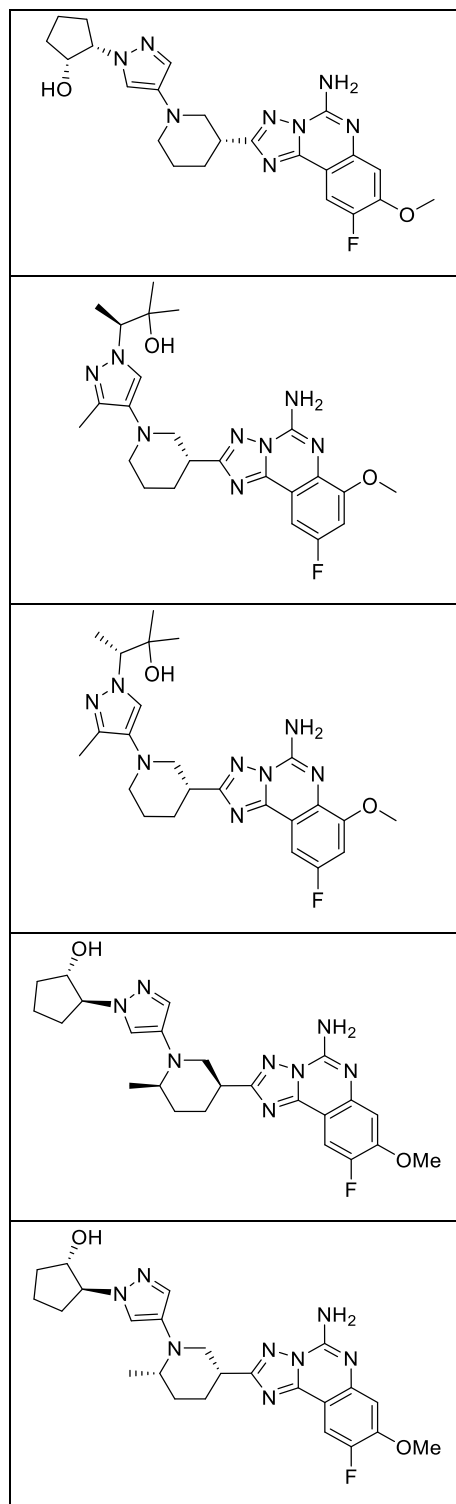
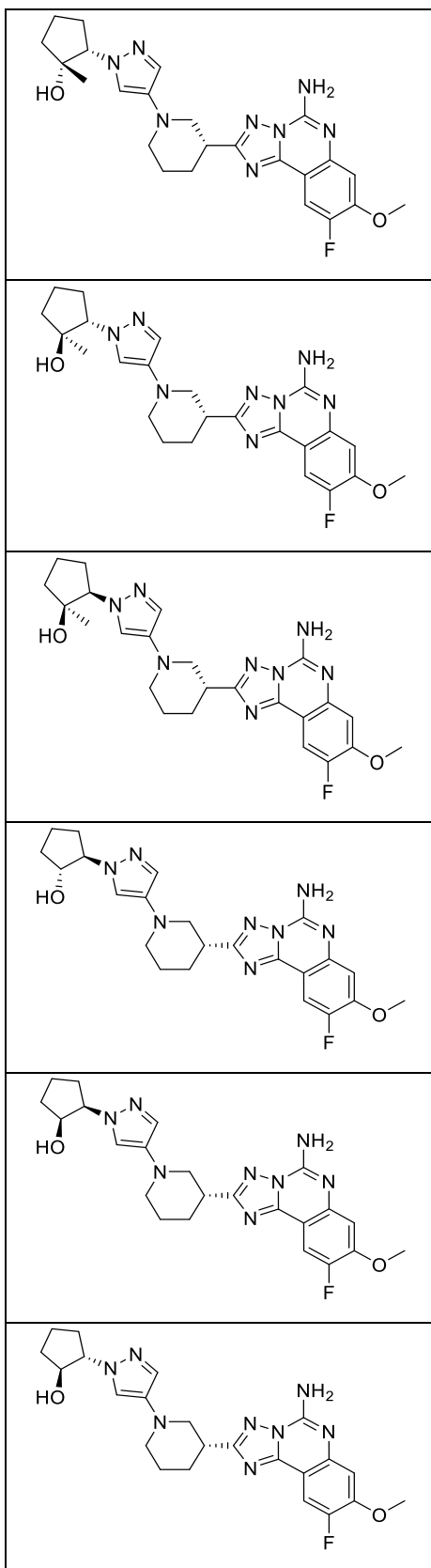


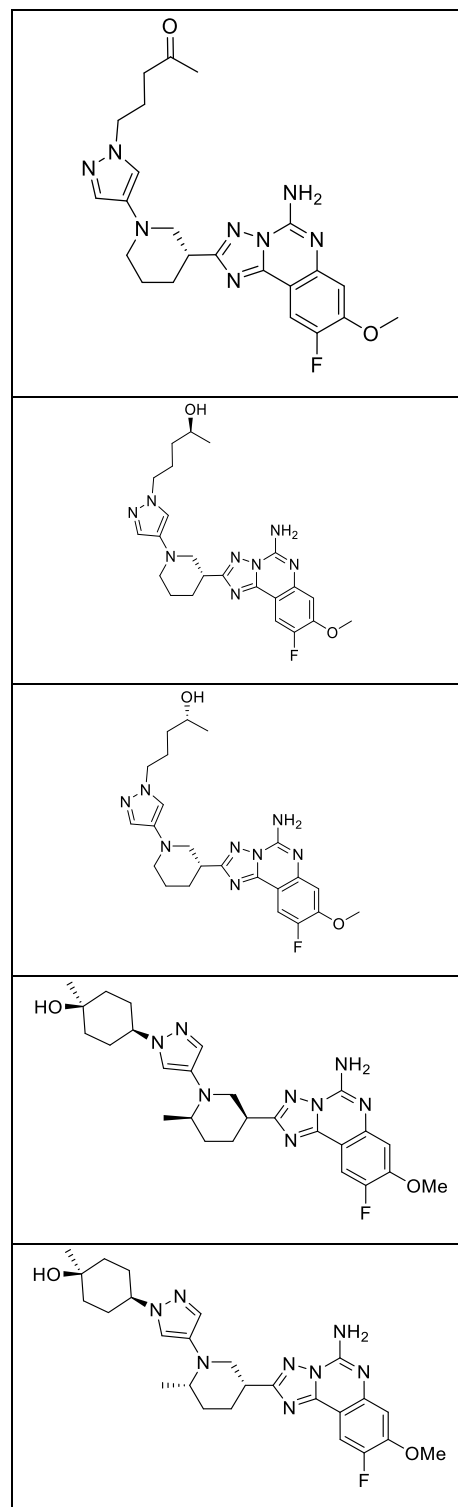
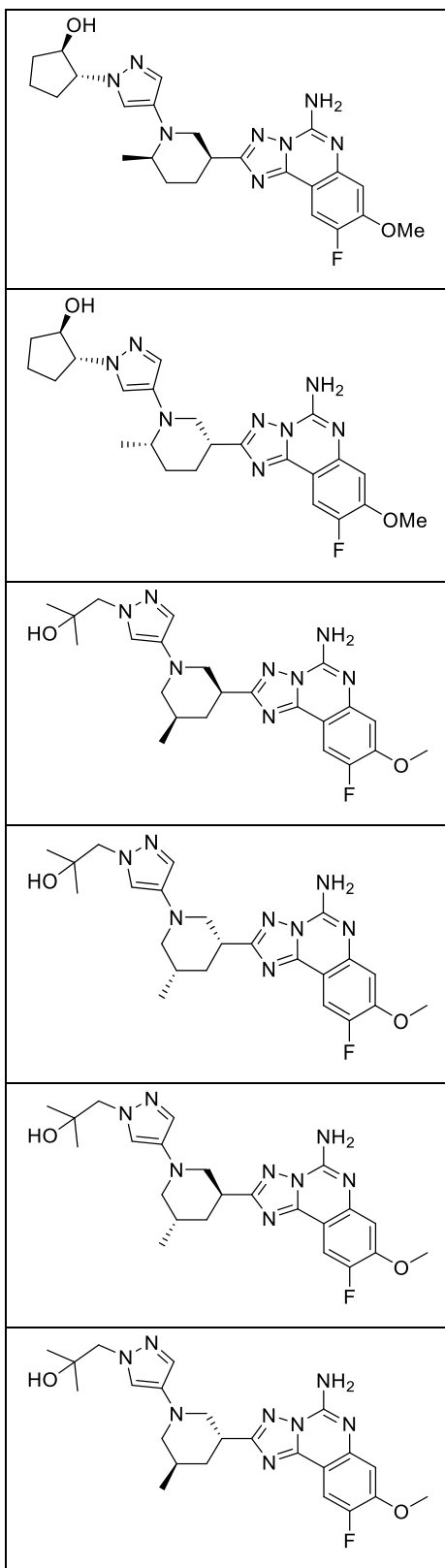


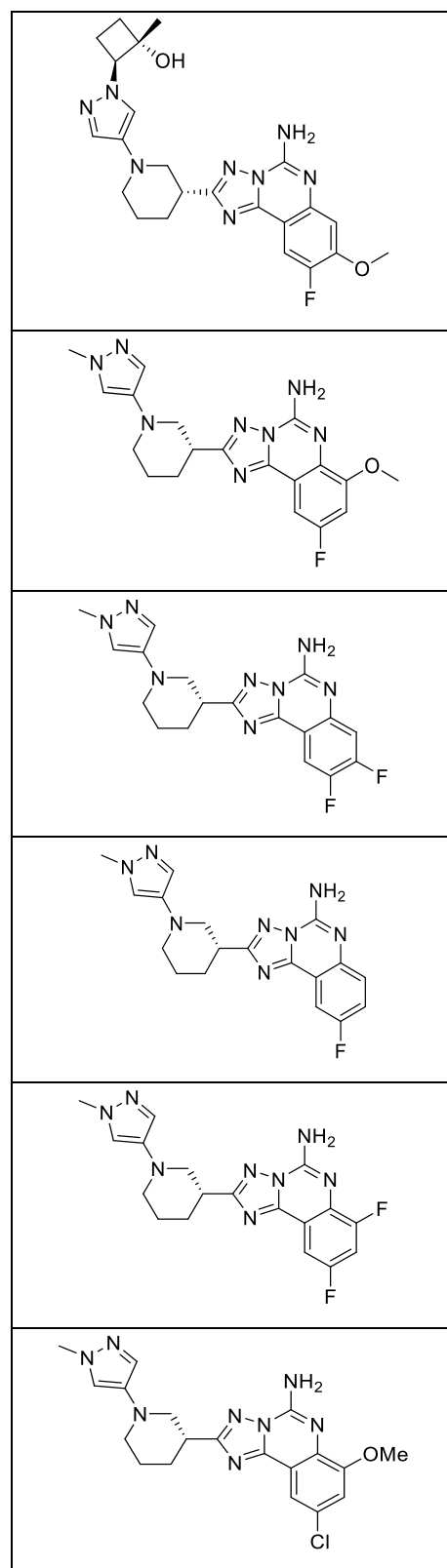
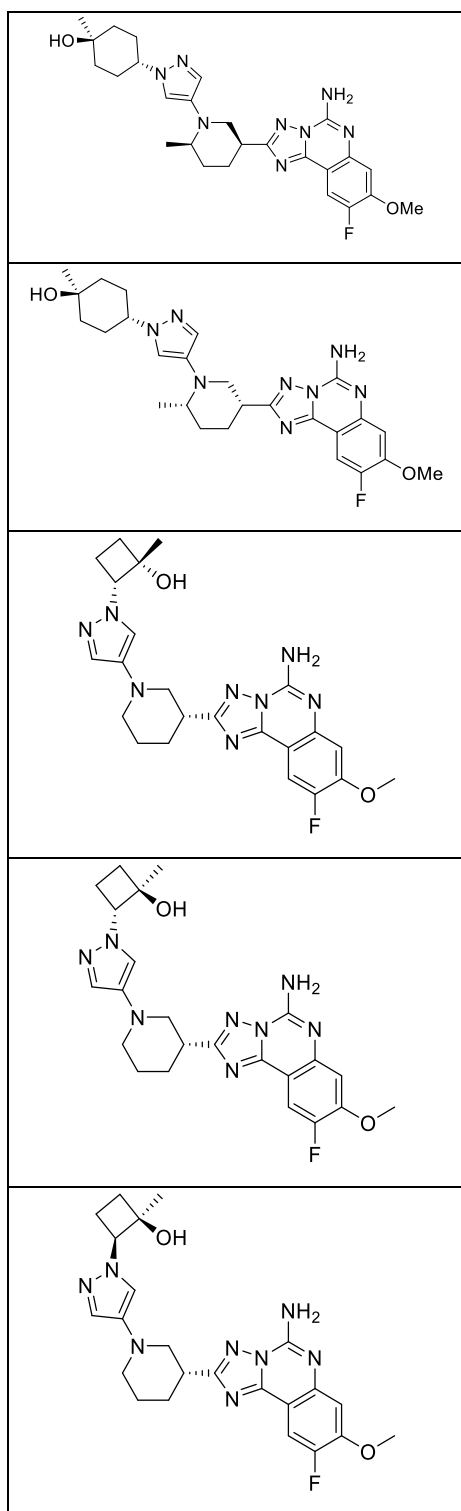


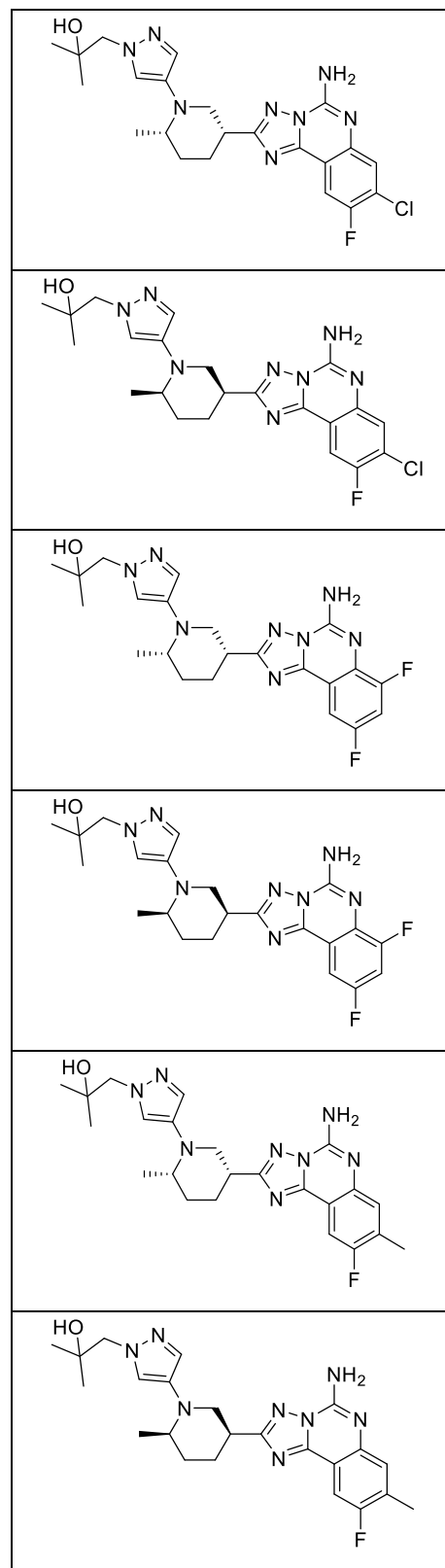
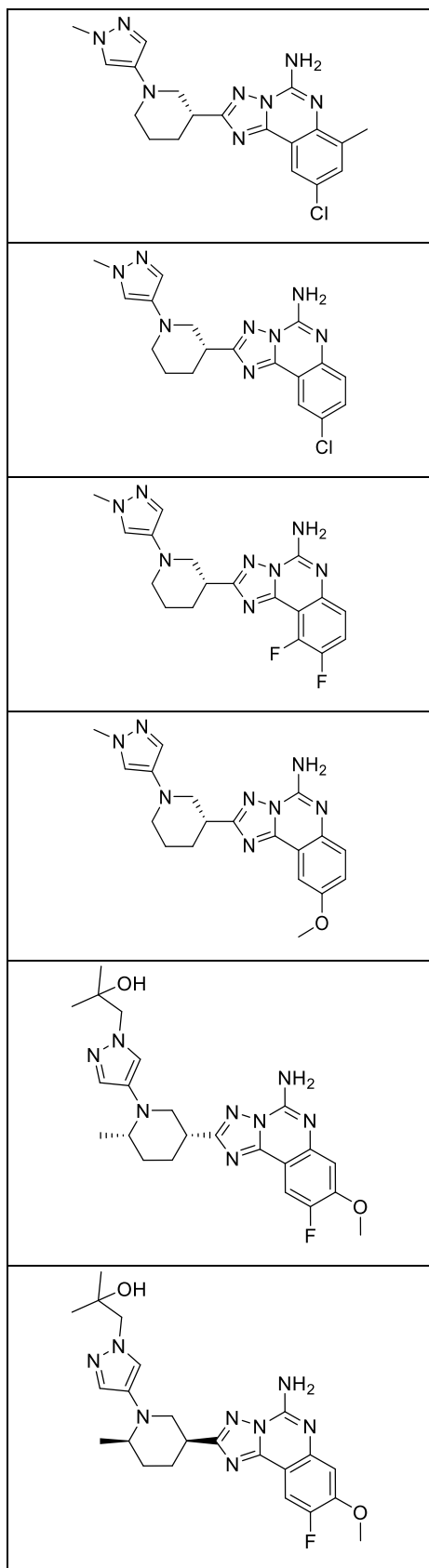


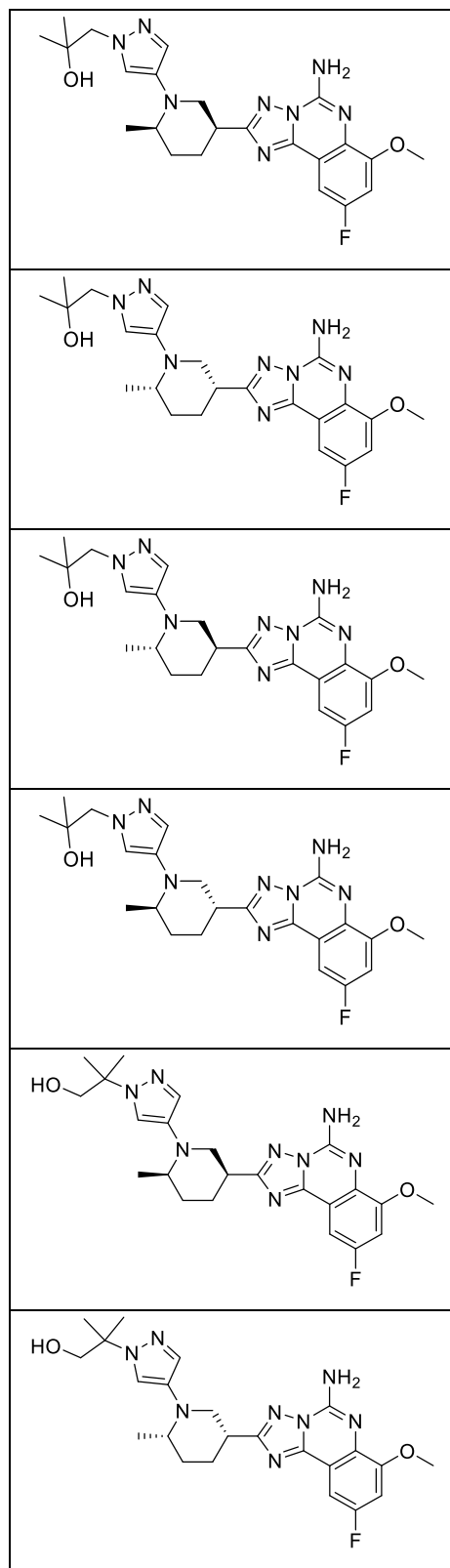
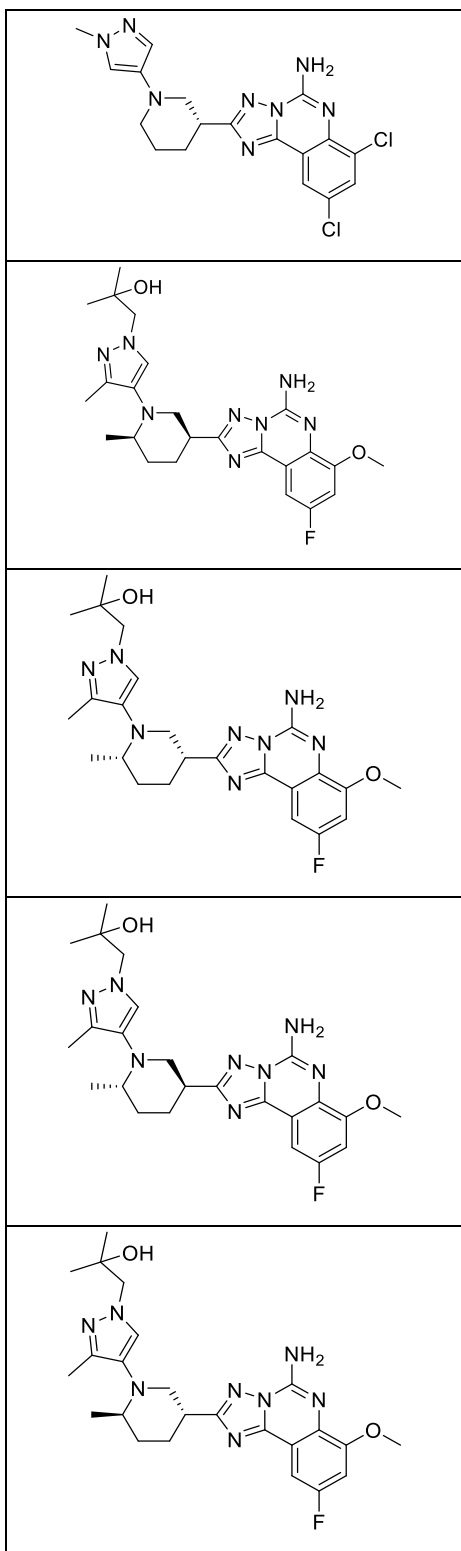


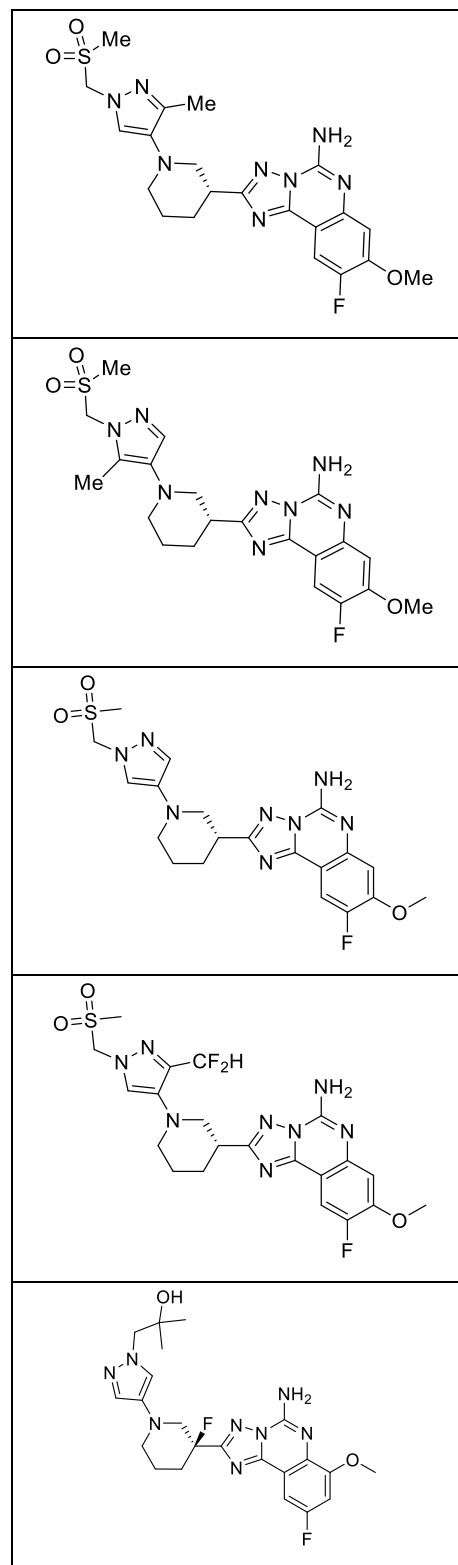
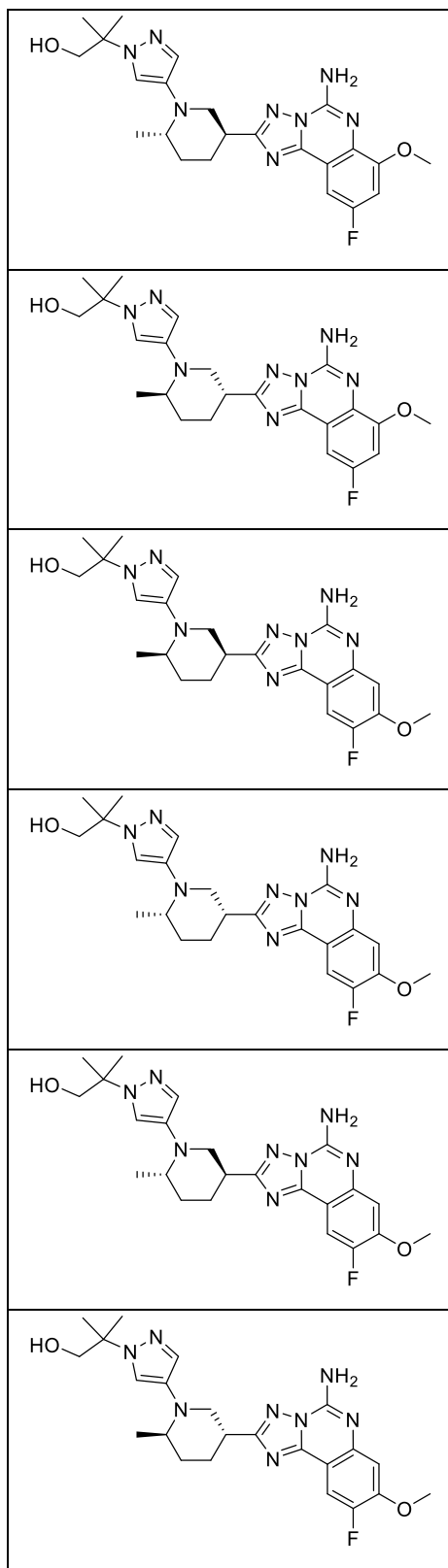


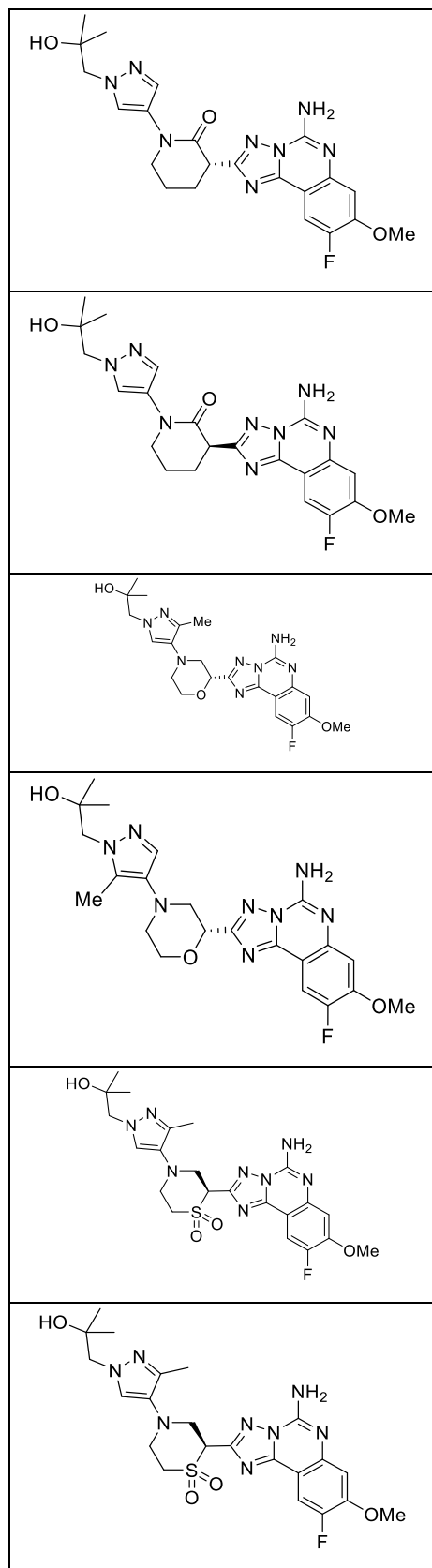
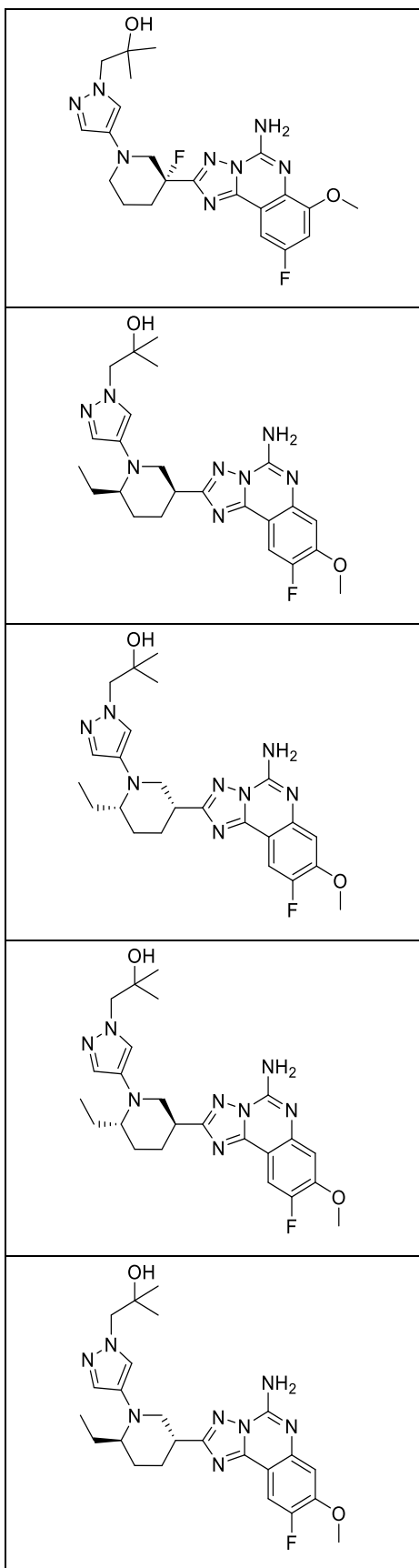


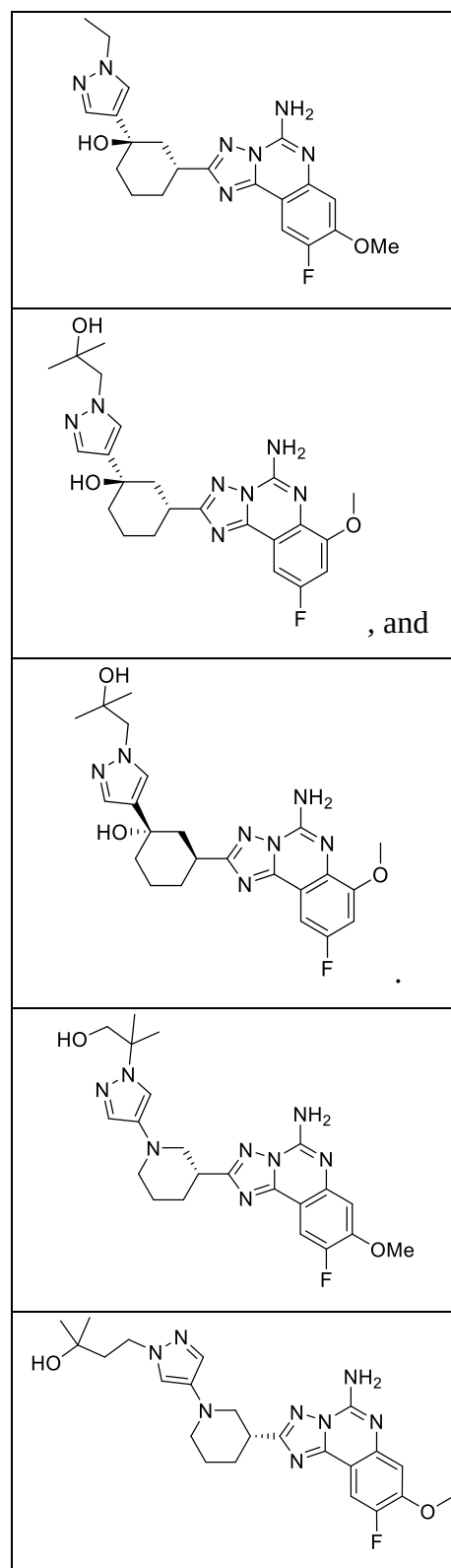
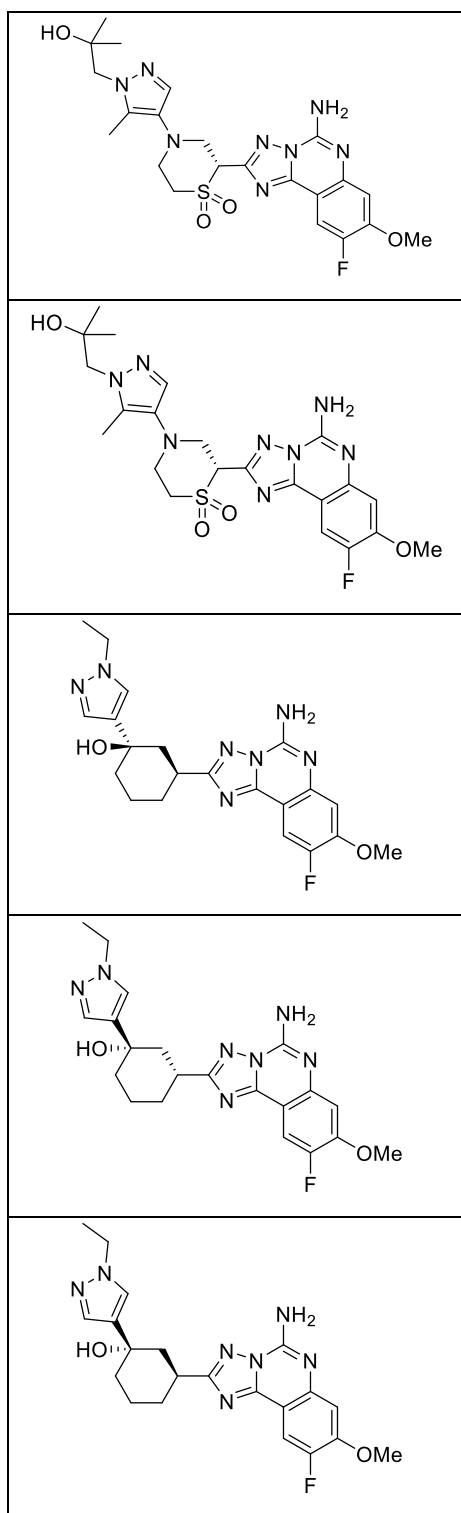


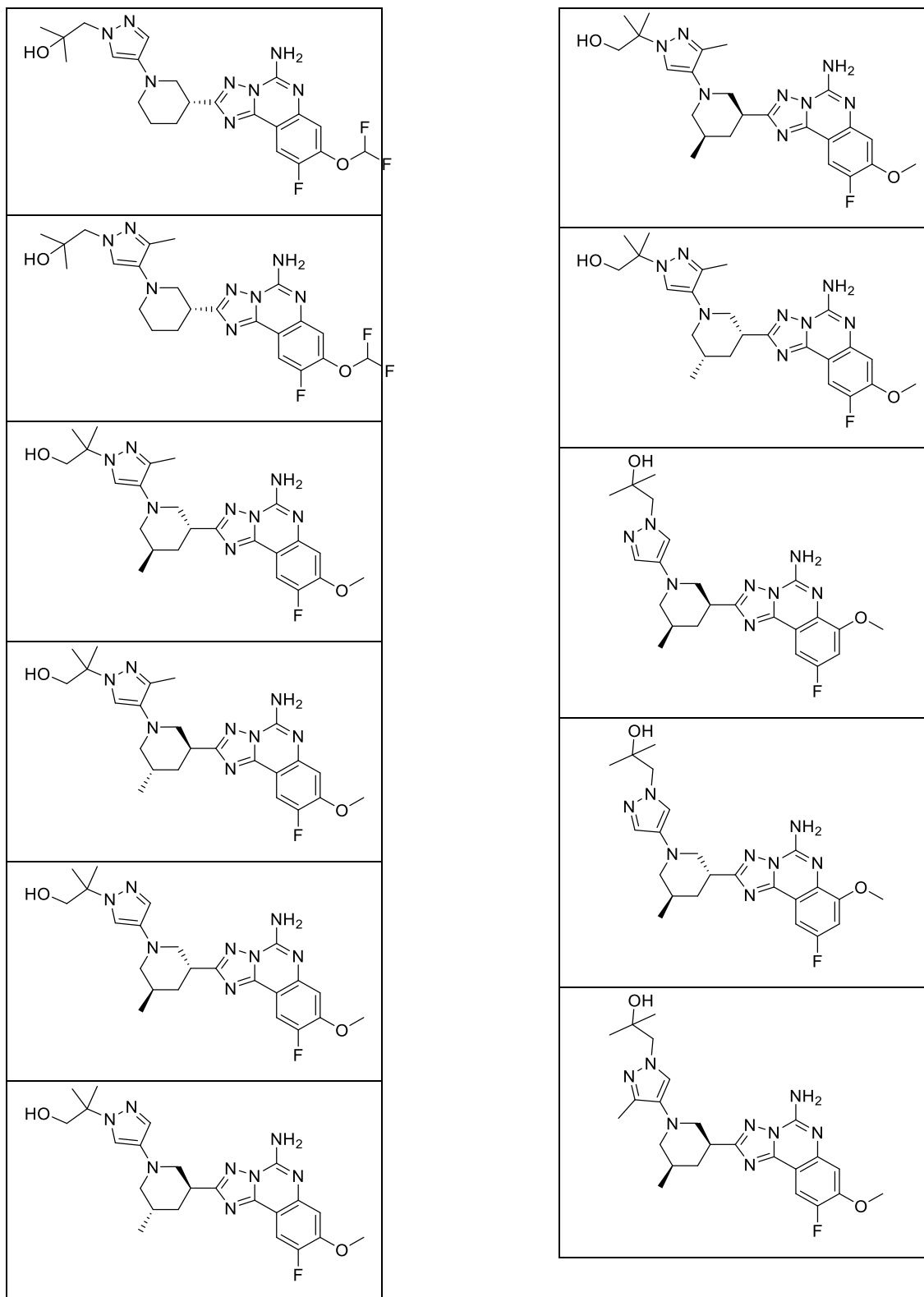


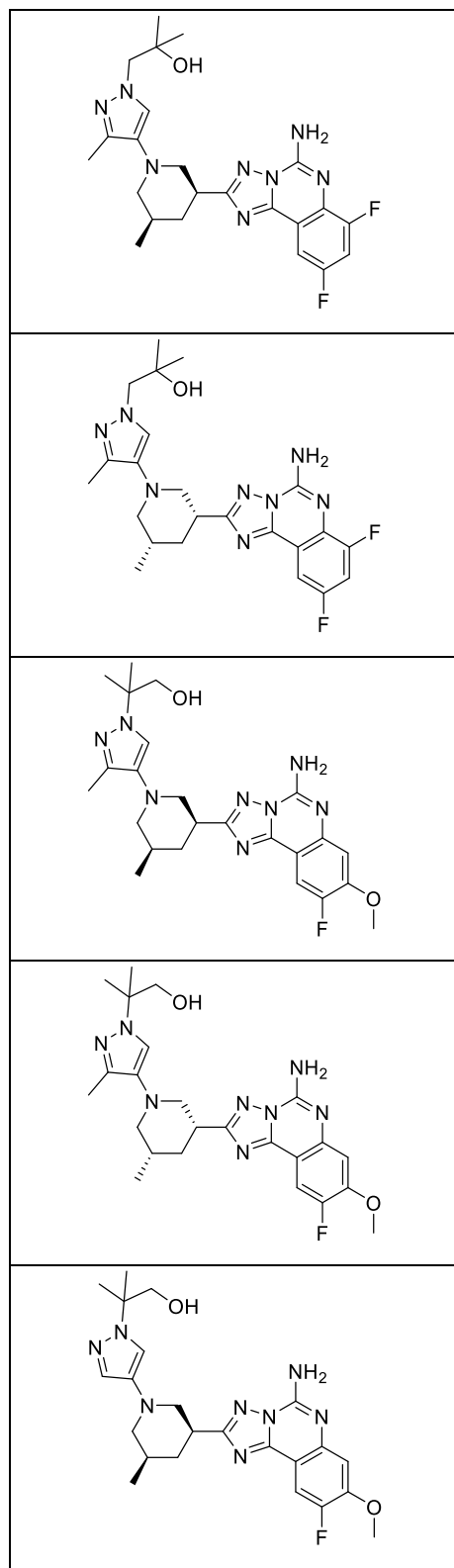
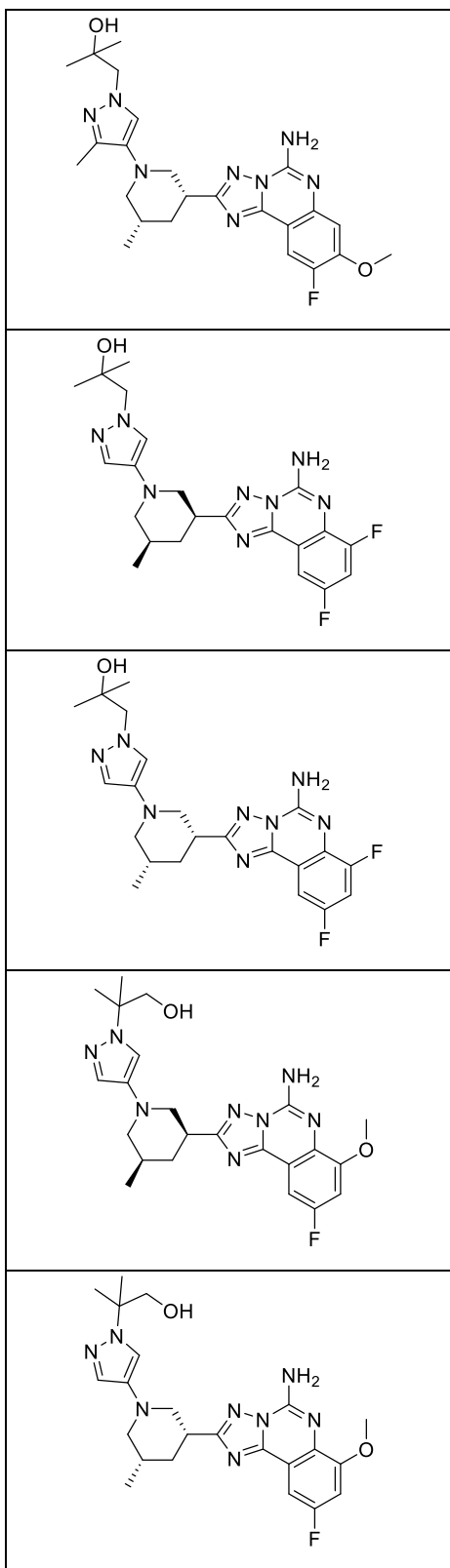


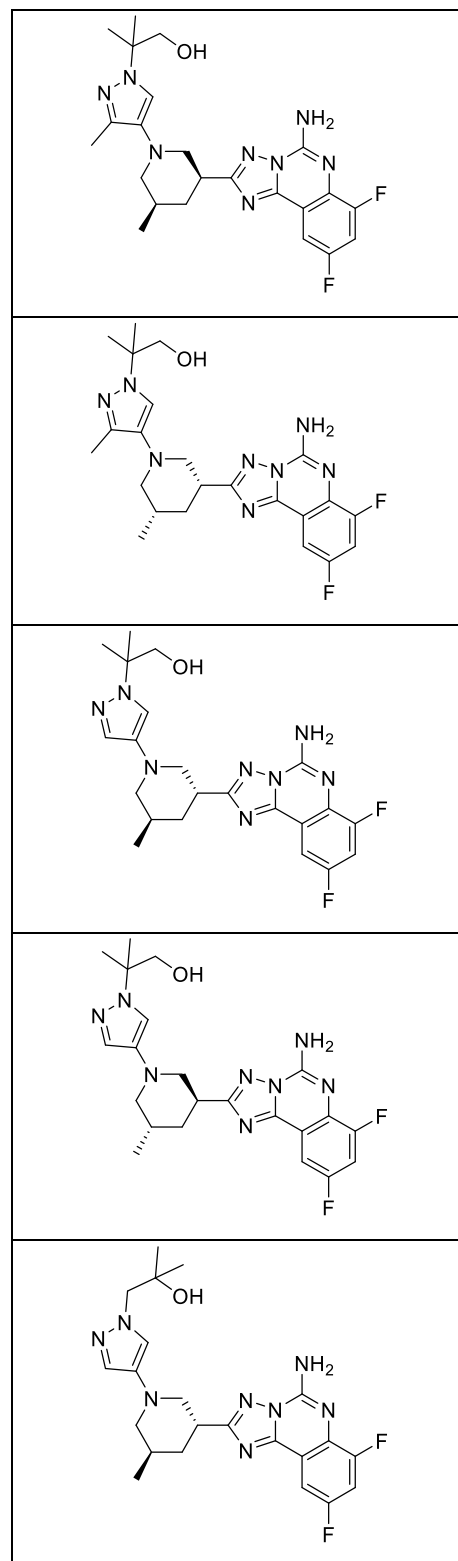
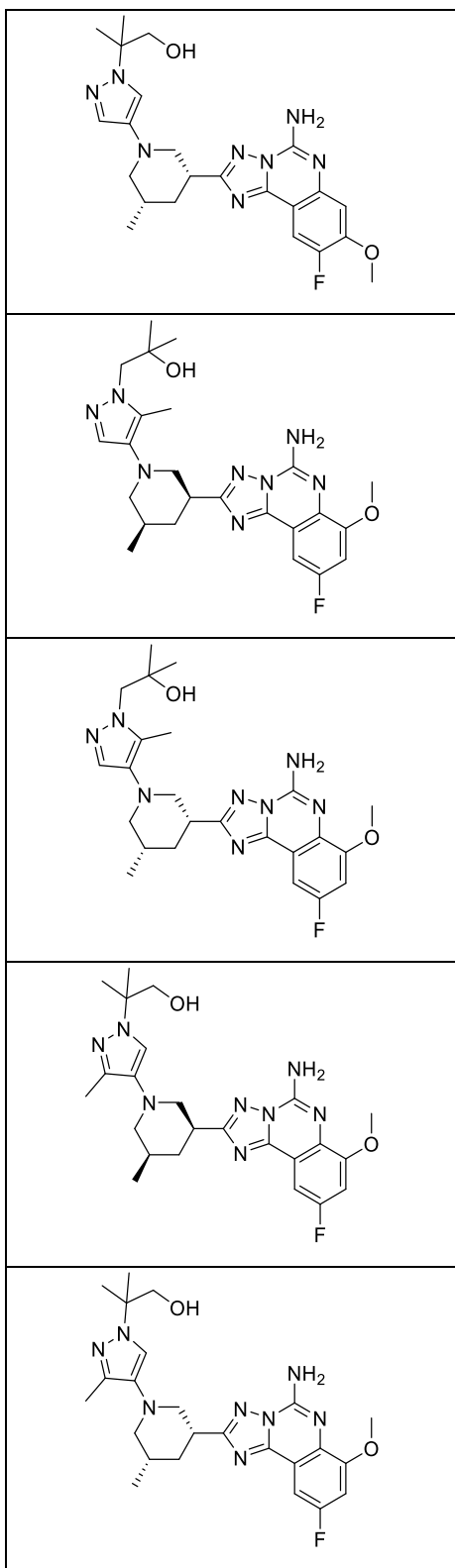


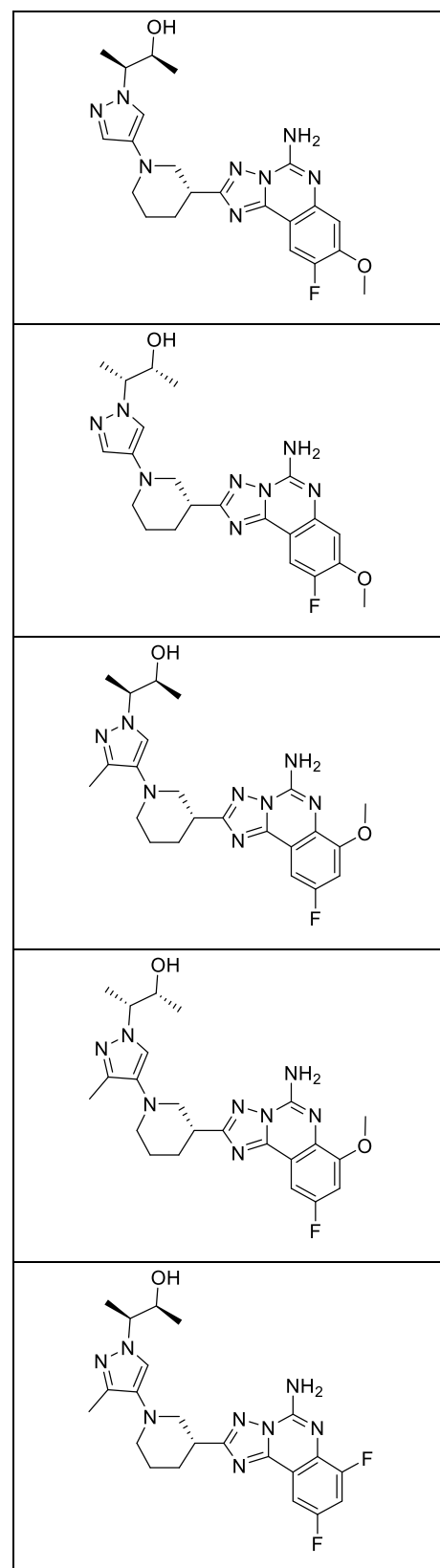
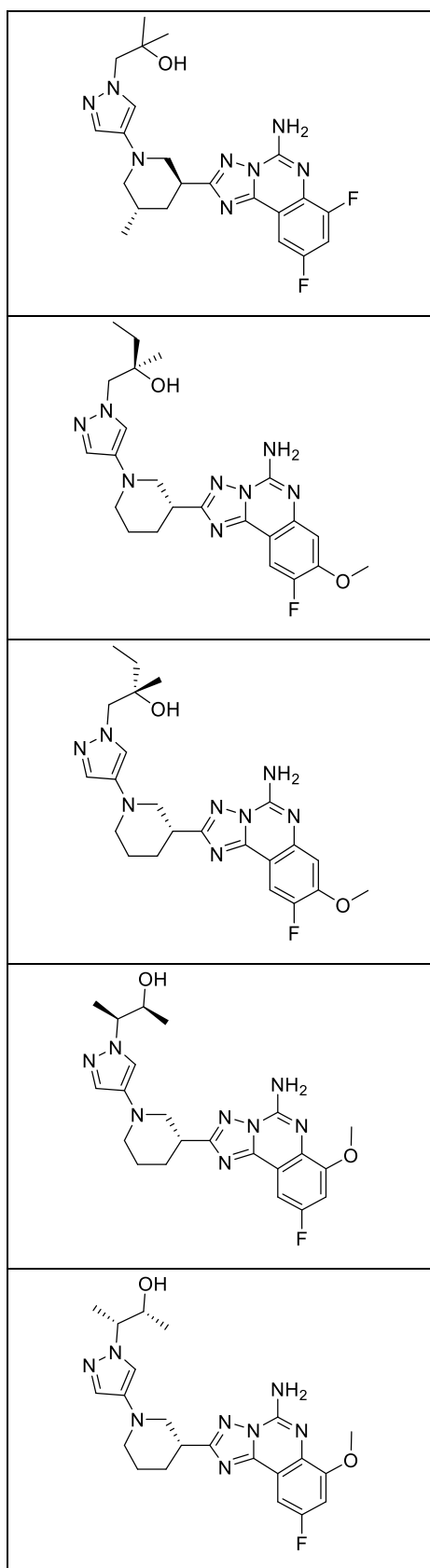


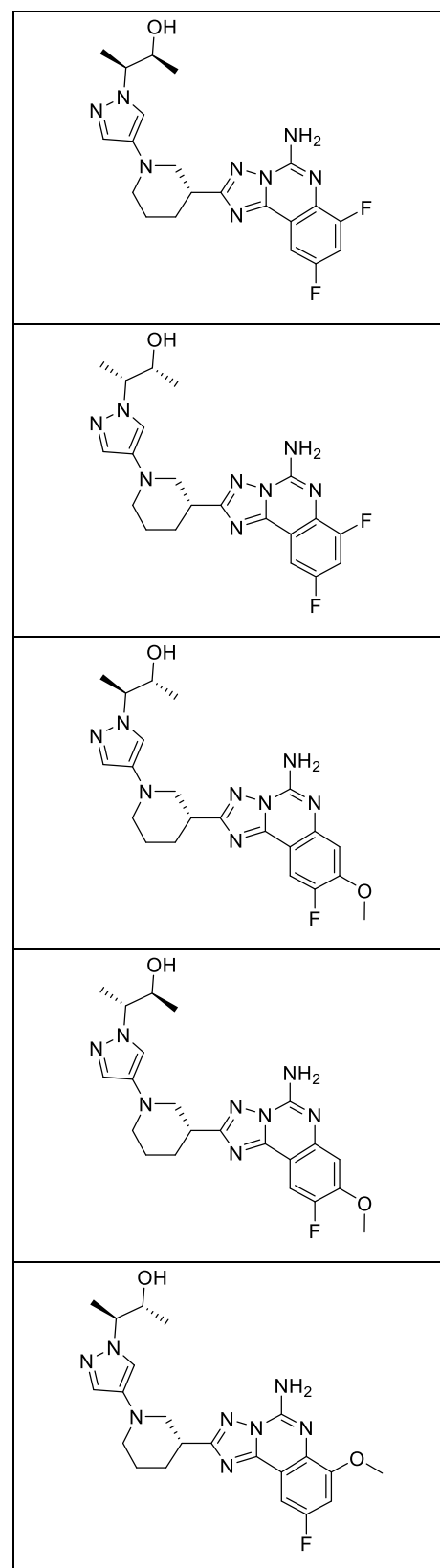
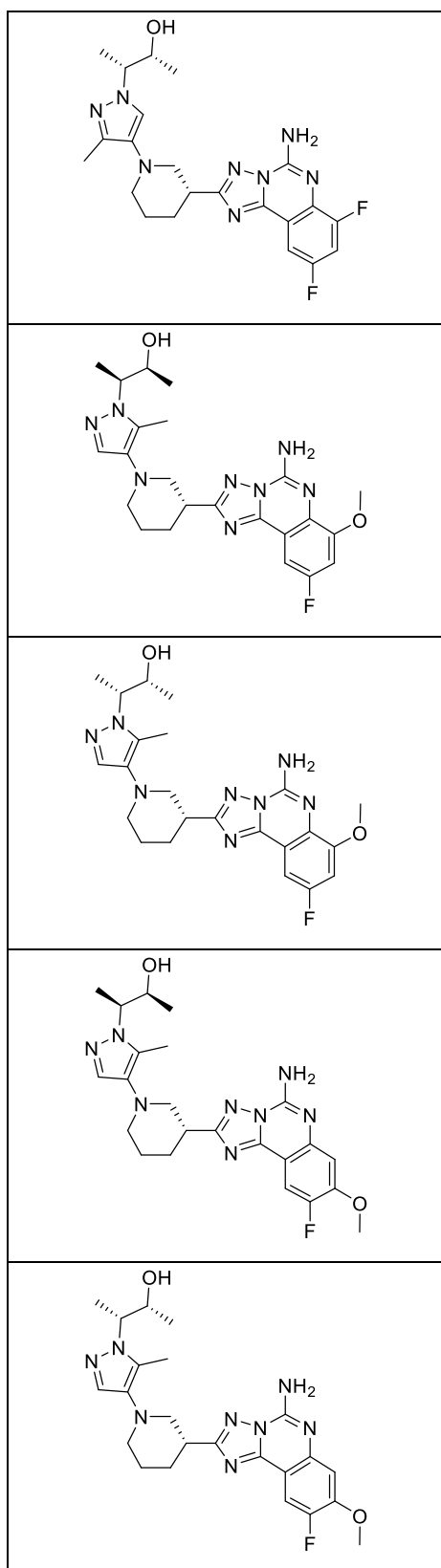


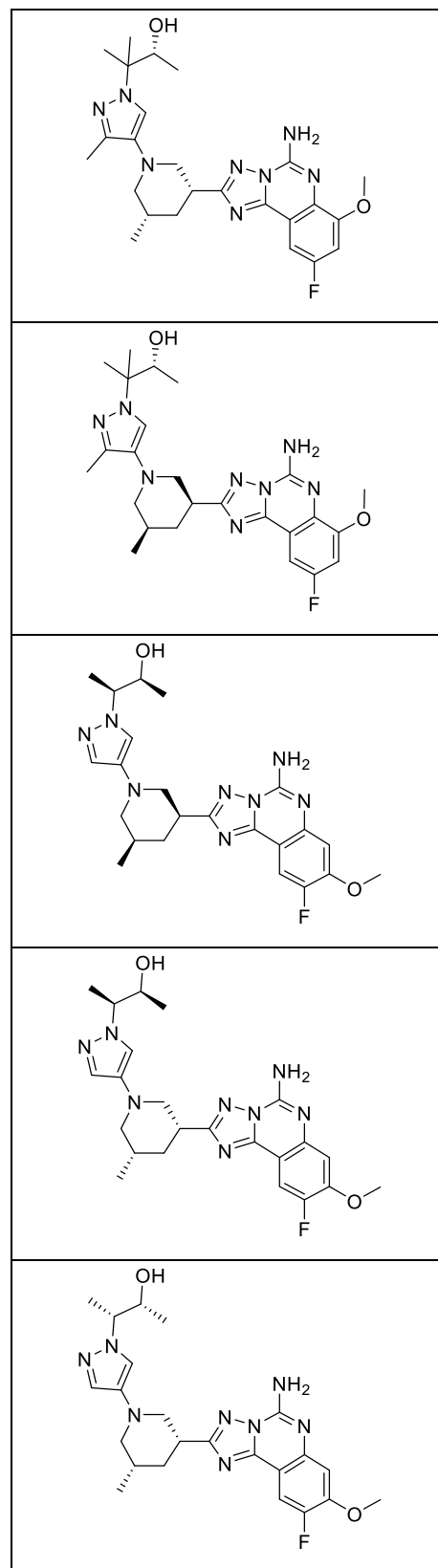
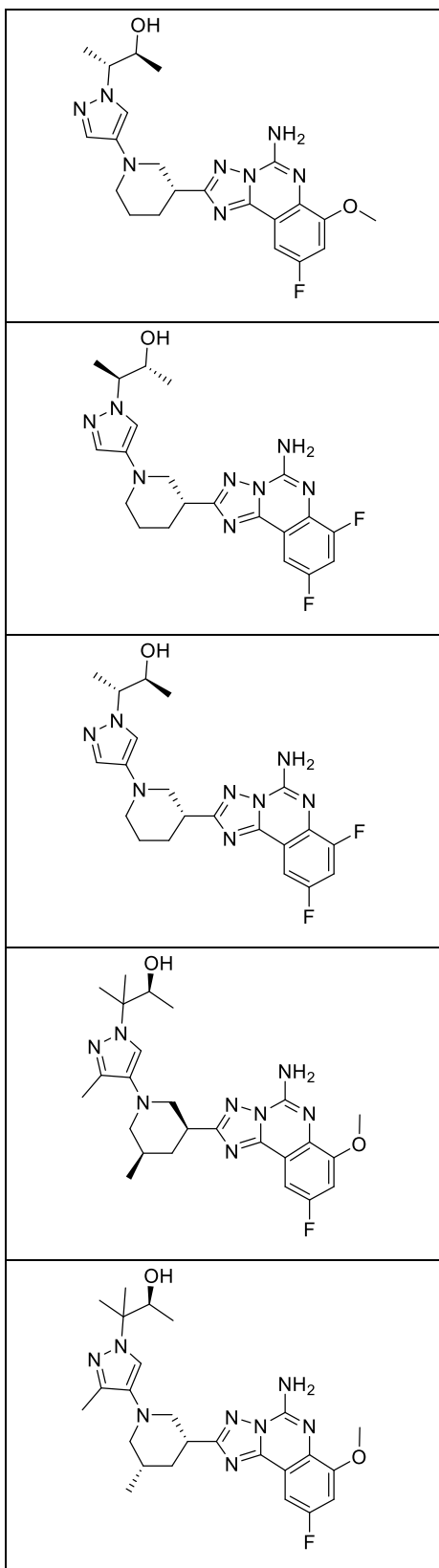


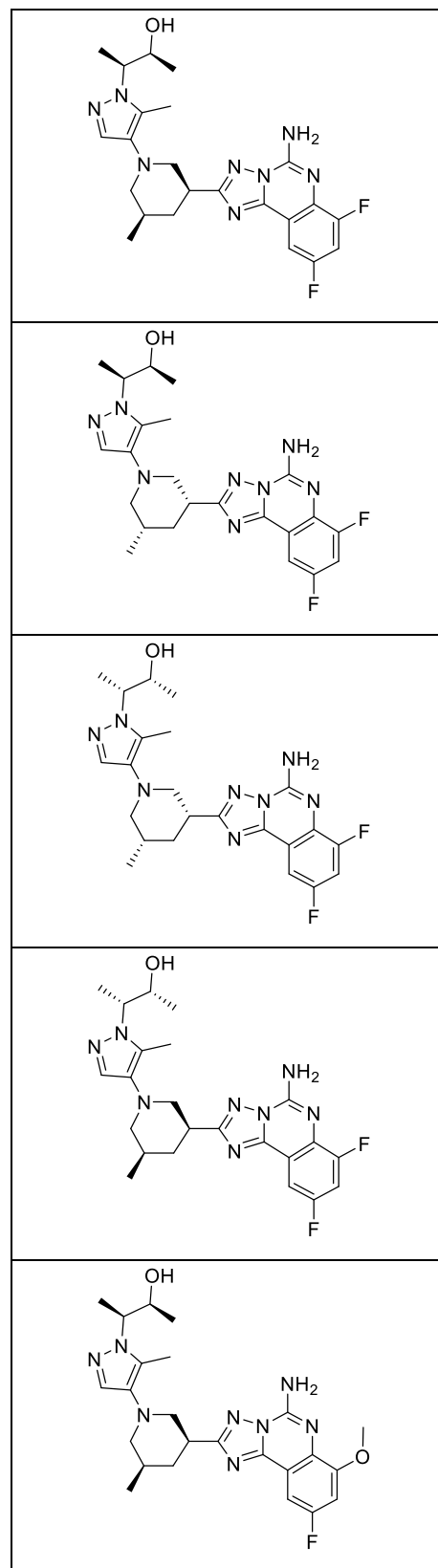
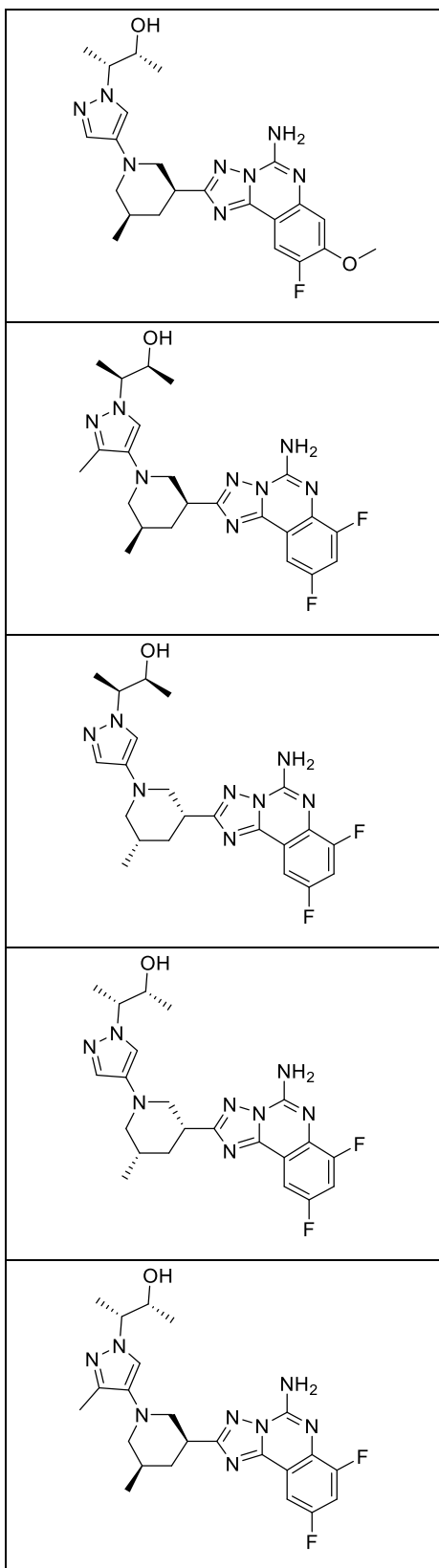


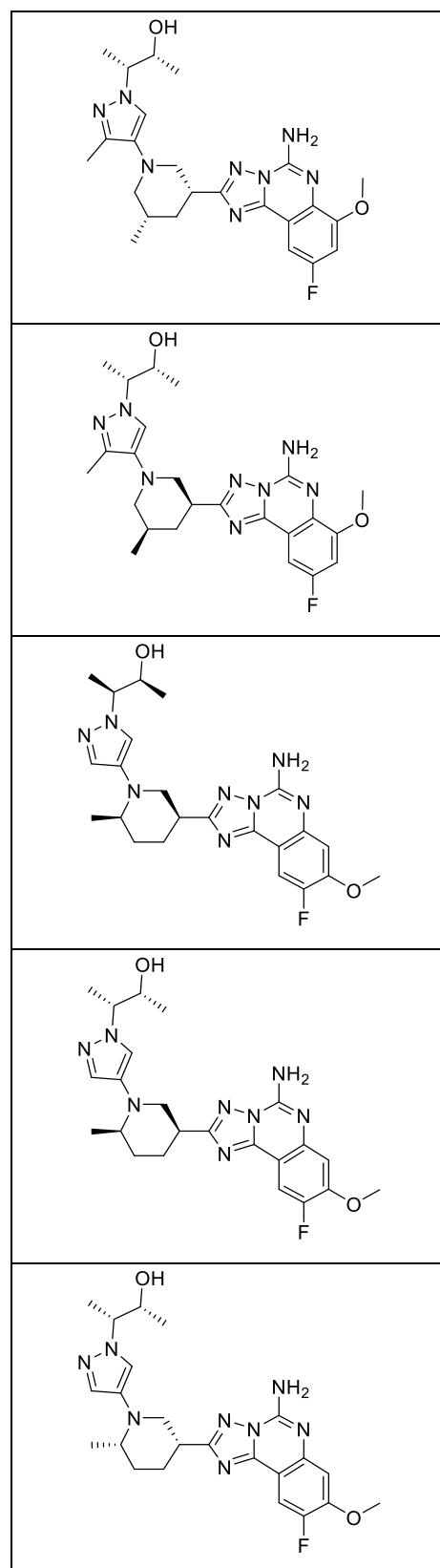
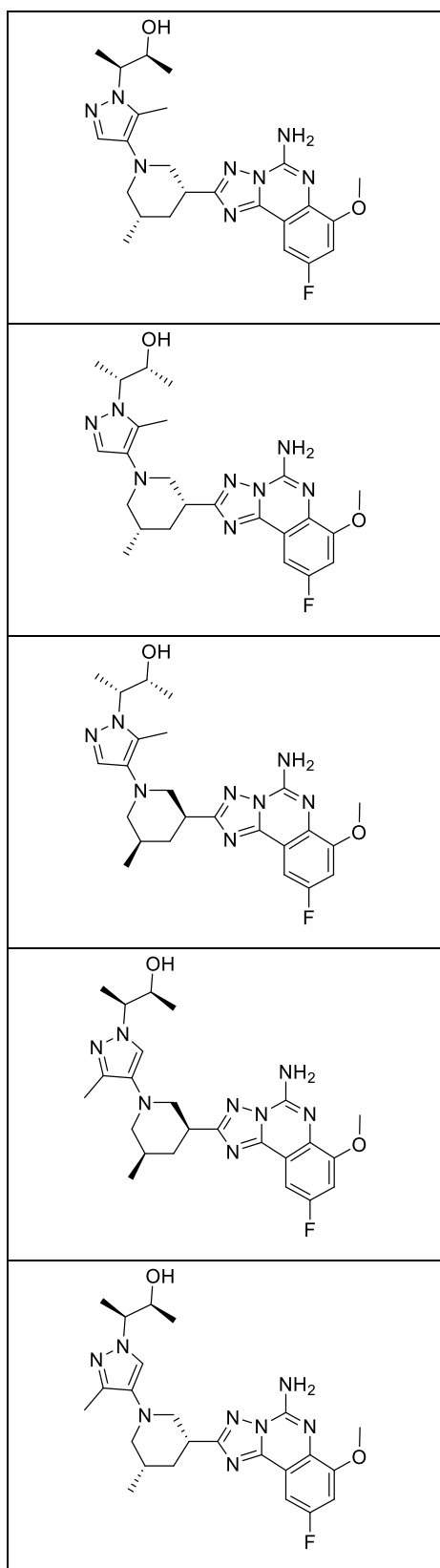


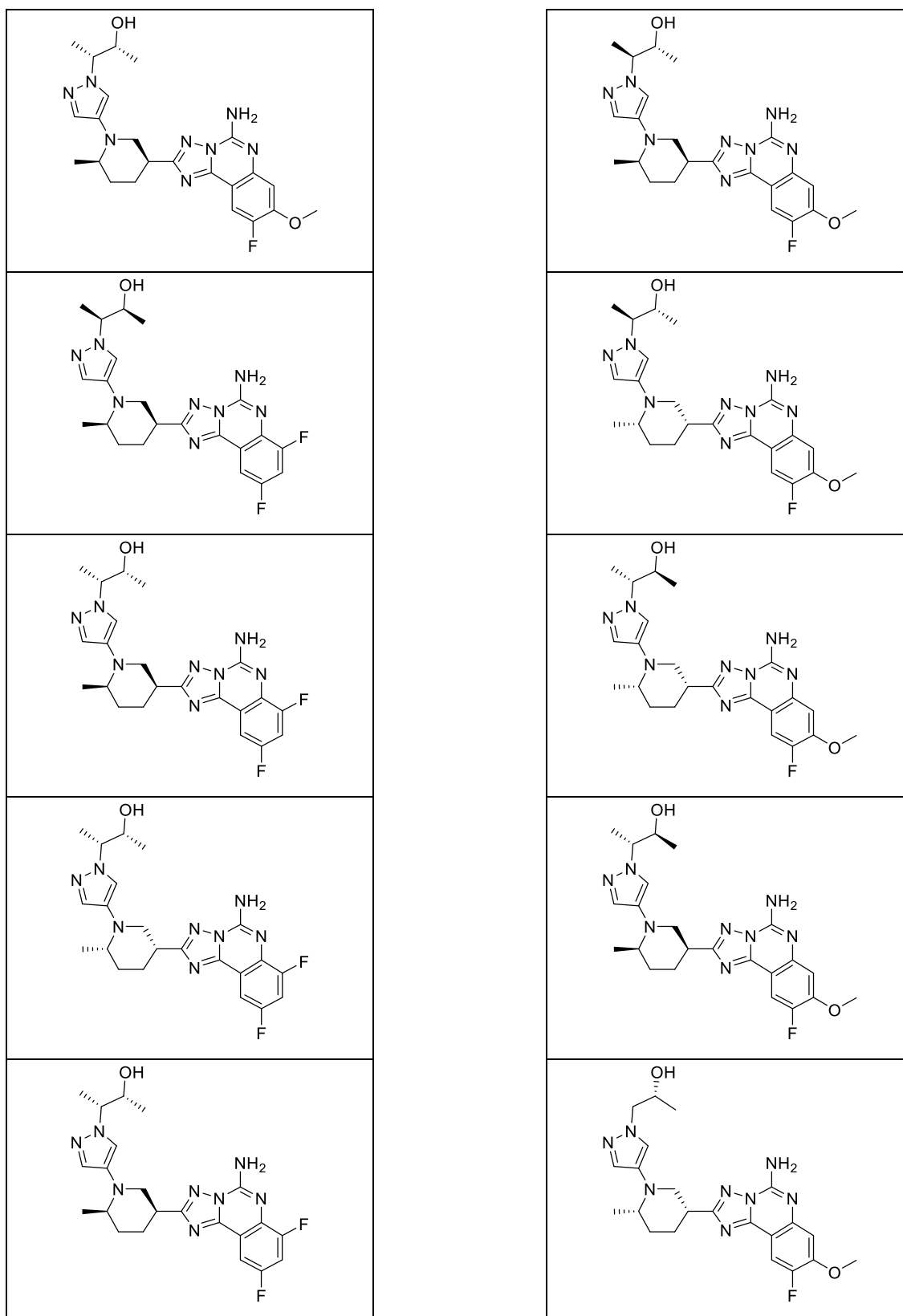


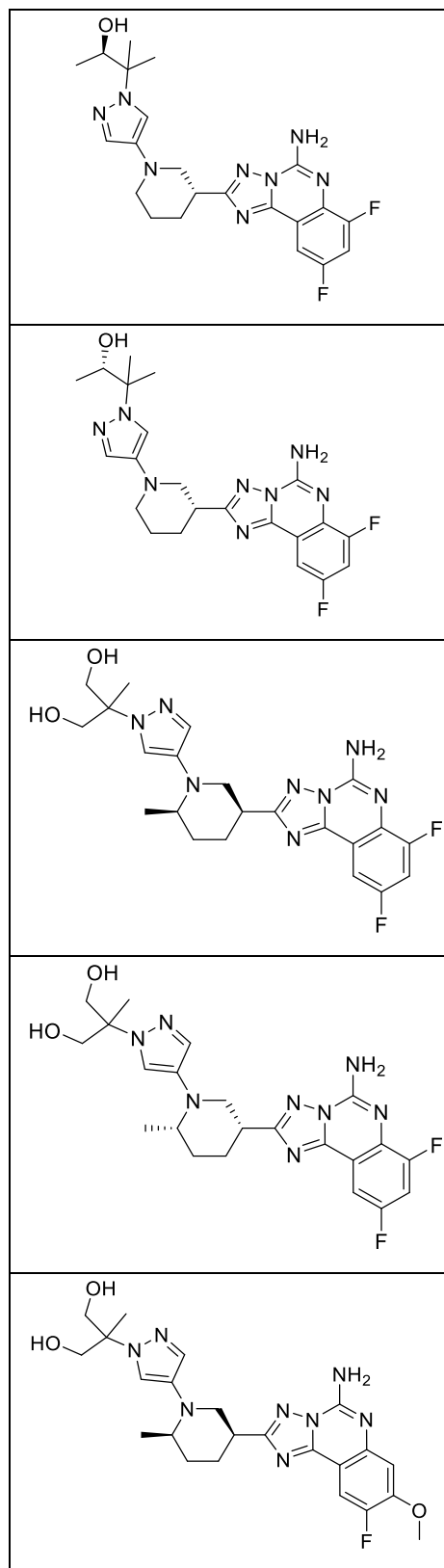
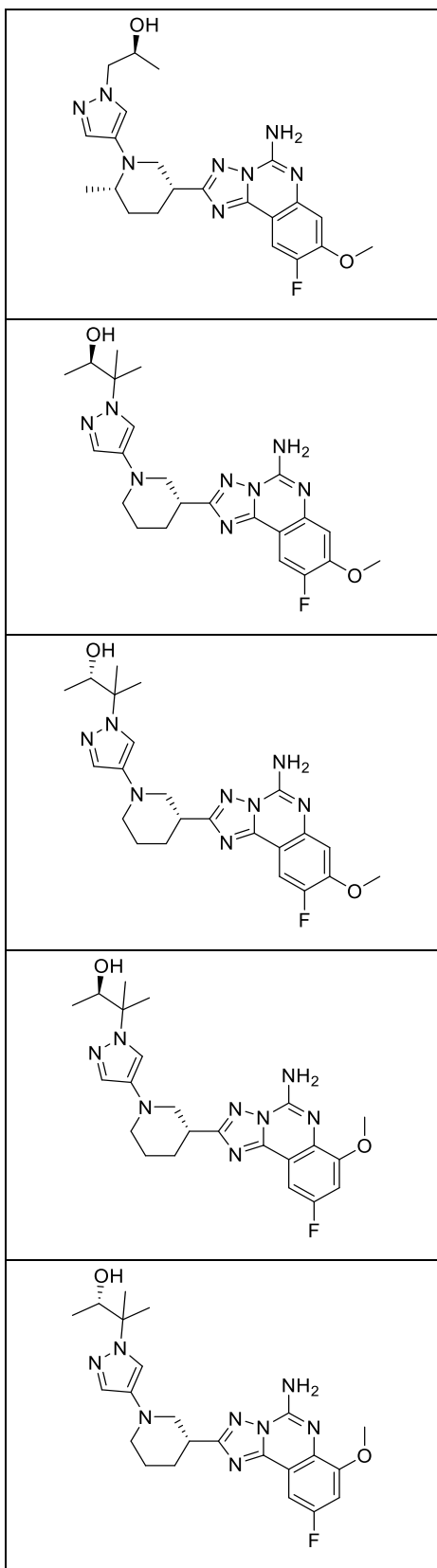


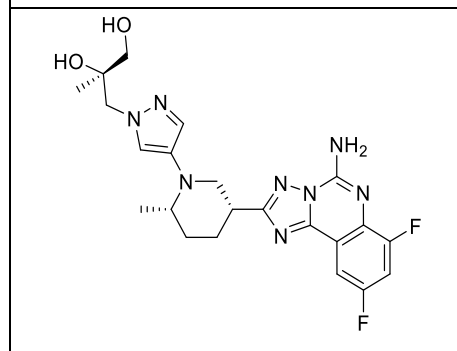
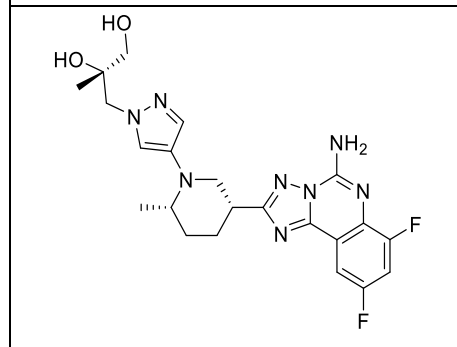
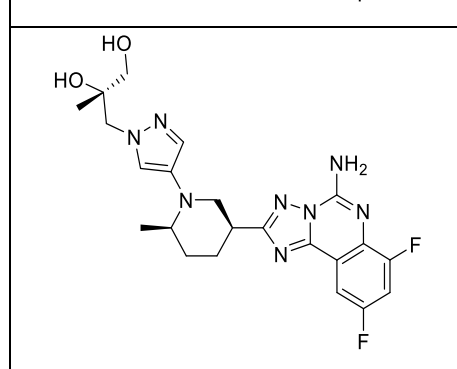
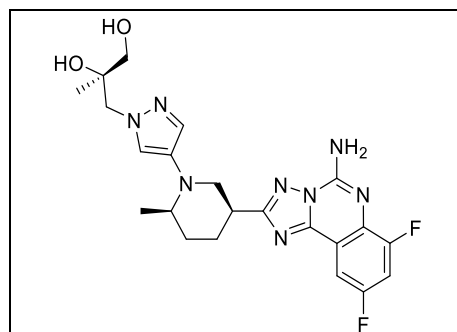
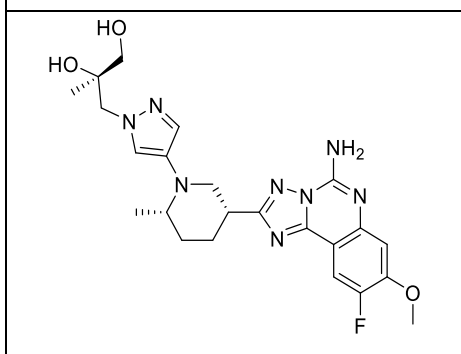
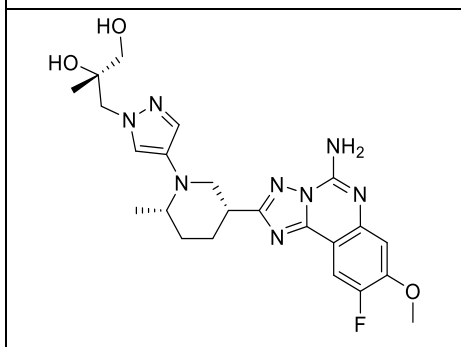
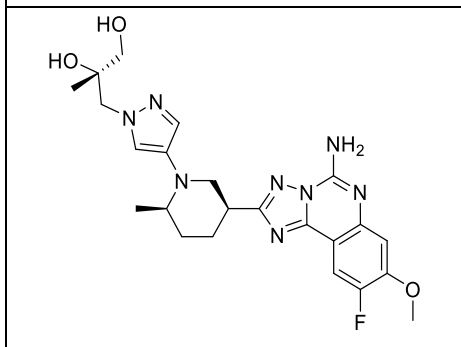
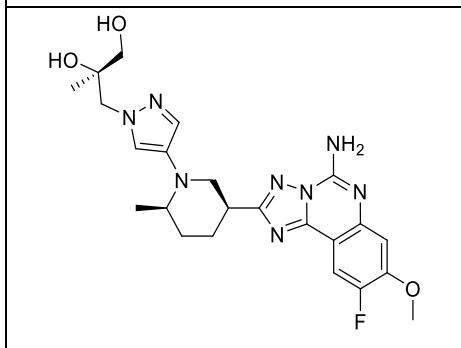
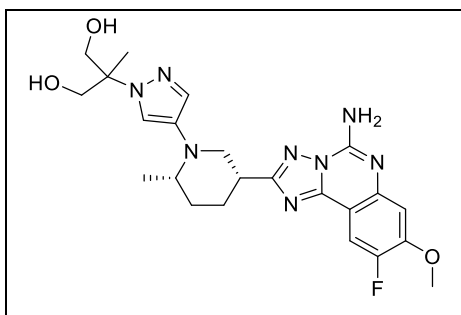


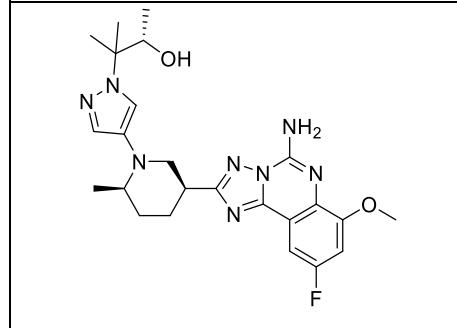
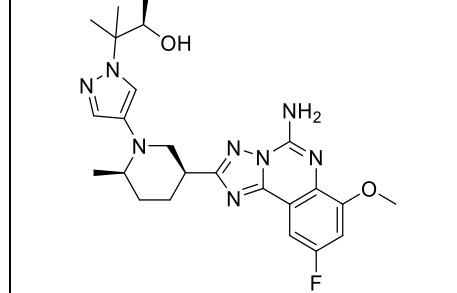
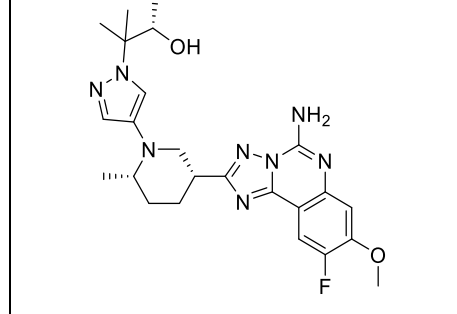
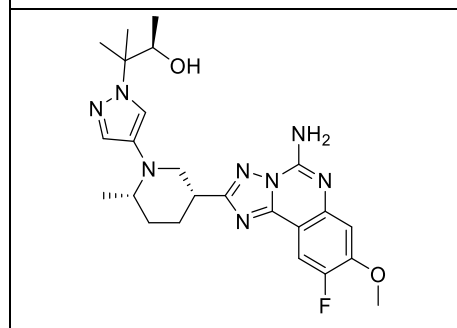
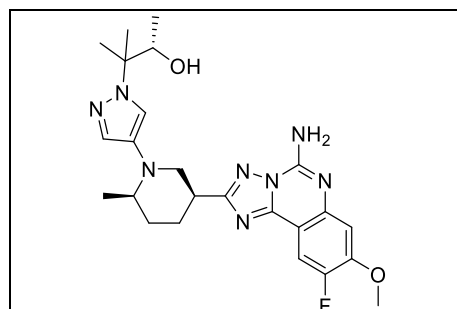
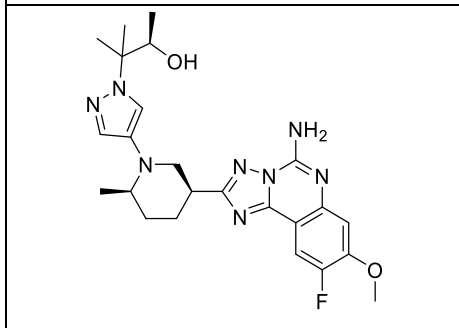
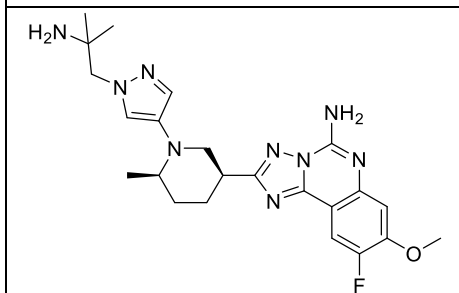
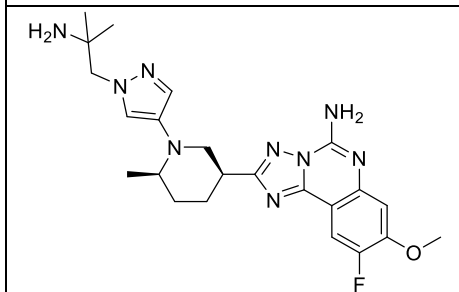
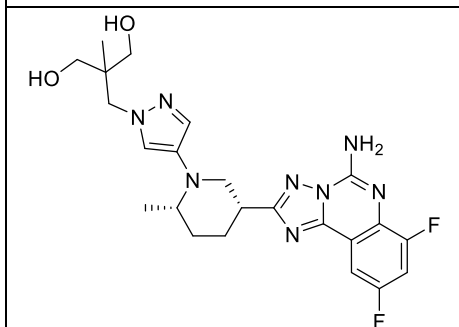
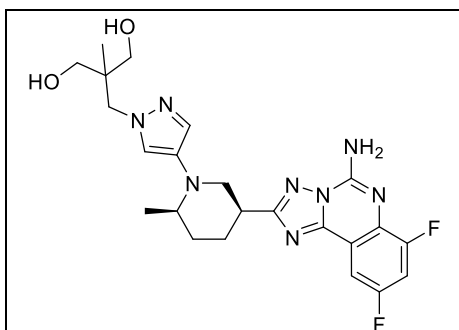


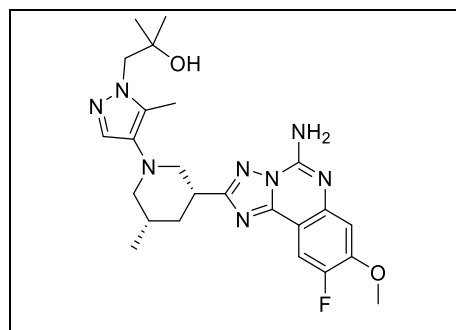
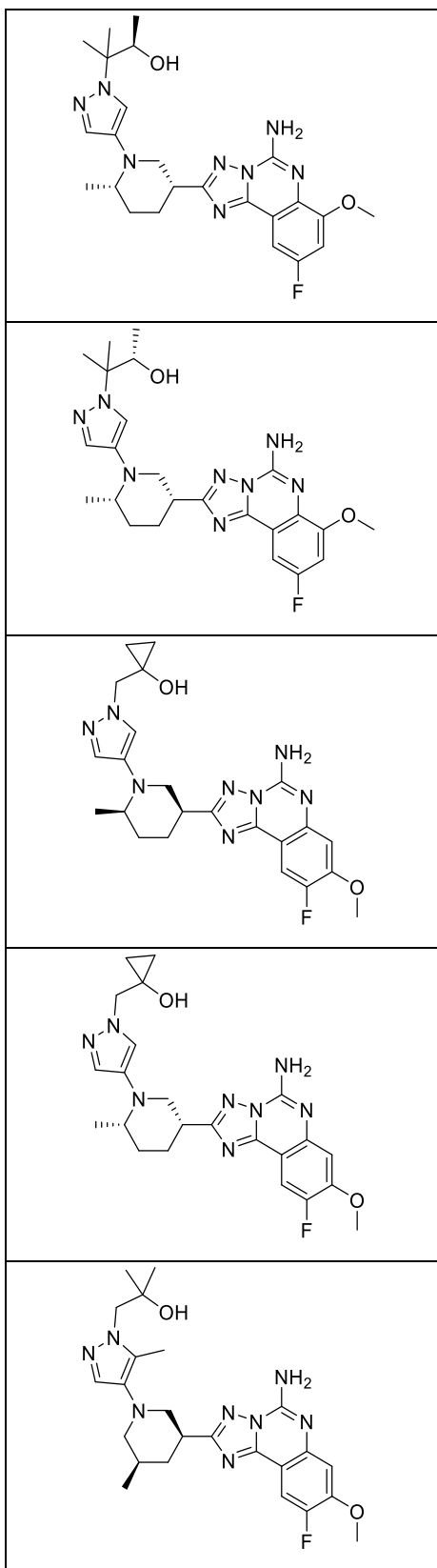




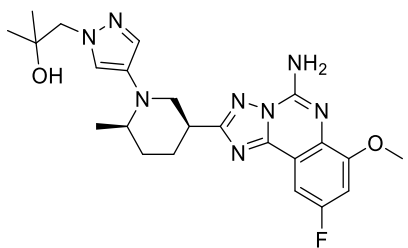




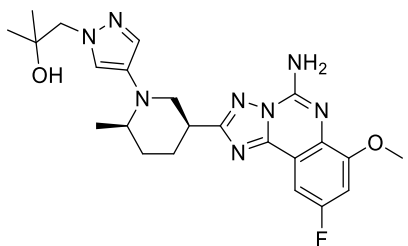




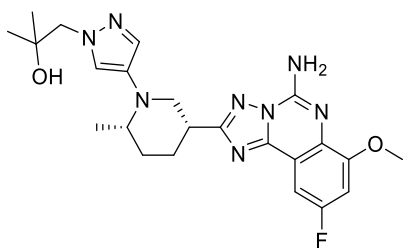
11. A pharmaceutical composition comprising a compound of any of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
12. Use of the compound of any of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.
13. The use of claim 12, wherein said cancer is selected from melanoma, head & neck cancer, classical Hodgkin lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, primary mediastinal large-B-cell lymphoma, microsatellite instability-high cancer, non-small cell lung cancer, hepatocellular carcinoma, clear cell kidney cancer, colorectal cancer, breast cancer, squamous cell lung cancer, basal carcinoma, sarcoma, bladder cancer, endometrial cancer, pancreatic cancer, liver cancer, gastrointestinal cancer, multiple myeloma, renal cancer, mesothelioma, ovarian cancer, anal cancer, biliary tract cancer, esophageal cancer, salivary cancer, and prostate cancer, and metastatic castration resistant prostate cancer.
14. The use of claim 13, wherein said compound, or a pharmaceutically acceptable salt thereof, is to be administered in combination with another therapeutic agent.
15. The use of claim 14, wherein said additional therapeutic agent is a PD-1 antagonist.
16. The use of claim 15, wherein said additional therapeutic agent is selected from pembrolizumab nivolumab, atezolizumab, durvalumab, and avelumab.
17. The use of claim 15, wherein said additional therapeutic agent is pembrolizumab.
18. The compound of any of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in therapy.
19. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



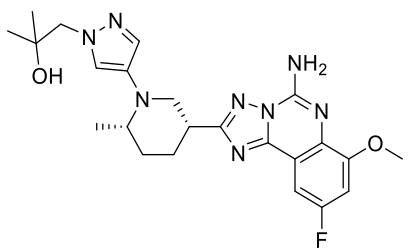
20. A compound, wherein the compound is:



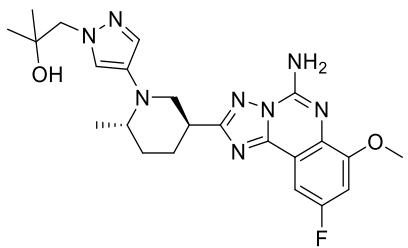
21. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is:



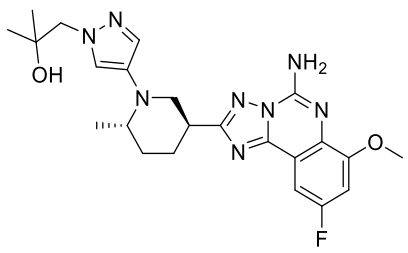
22. A compound, wherein the compound is:



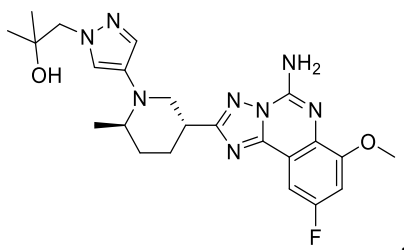
23. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is:



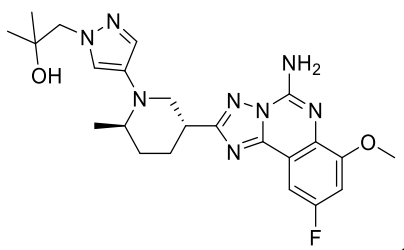
24. A compound, wherein the compound is:



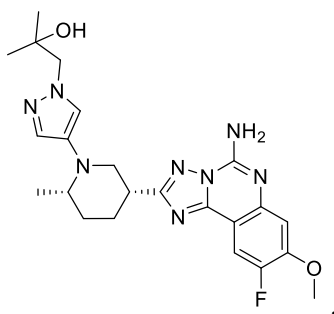
25. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is:



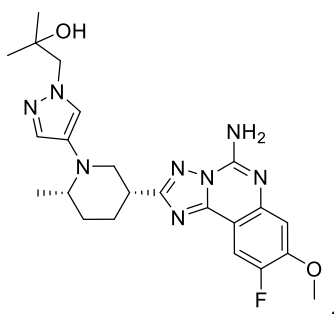
26. A compound, wherein the compound is:



27. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is:



28. A compound, wherein the compound is:



29. A pharmaceutical composition comprising a compound of any of claims 19 to 28, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
30. Use of the compound of any of claims 19 to 28, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.
31. The use of claim 30, wherein said cancer is selected from melanoma, head & neck cancer, classical Hodgkin lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, primary mediastinal large-B-cell lymphoma, microsatellite instability-high cancer, non-small cell lung cancer, hepatocellular carcinoma, clear cell kidney cancer, colorectal cancer, breast cancer, squamous cell lung cancer, basal carcinoma, sarcoma, bladder cancer, endometrial cancer, pancreatic cancer, liver cancer, gastrointestinal cancer, multiple myeloma, renal cancer, mesothelioma, ovarian cancer, anal cancer, biliary tract cancer, esophageal cancer, salivary cancer, and prostate cancer, and metastatic castration resistant prostate cancer.
32. The use of claim 31, wherein said compound, or a pharmaceutically acceptable salt thereof, is to be administered in combination with another therapeutic agent.
33. The use of claim 32, wherein said additional therapeutic agent is a PD-1 antagonist.
34. The use of claim 33, wherein said additional therapeutic agent is selected from pembrolizumab nivolumab, atezolizumab, durvalumab, and avelumab.
35. The use of claim 34, wherein said additional therapeutic agent is pembrolizumab.
36. The compound of any of claims 19 to 28, or a pharmaceutically acceptable salt thereof, for use in therapy.