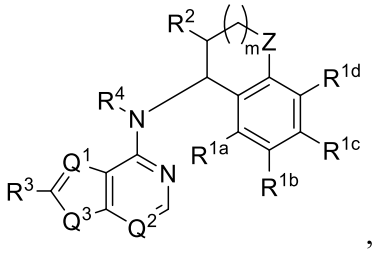
[0008] Despite the widespread prevalence of disorders associated with PINK1 pathway, compounds capable of selectively targeting this pathway and, thus, treating disorders associated with this pathway have remained elusive. Accordingly, there remains a need for compounds and compositions capable of modulating PINK1 kinase activity and methods of making and using same.

SUMMARY

[0009] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in some embodiments, relates to adenine compounds useful in the treatment of disorders associated with PINK1 kinase activity such as, for example, a neurodegenerative disease, a mitochondrial disease, fibrosis, and/or cardiomyopathy.

[0010] Thus, in an aspect, there is provided herein are compounds having a structure represented by a formula:



,

wherein m is 0 or 1; wherein each of Q^1 and Q^2 is independently N or CH; wherein Q^3 is CH_2 or NH; wherein Z is $CR^{11a}R^{11b}$, NR^{12}, or O; wherein each of R^{11a} and R^{11b}, when present, is independently selected from hydrogen, halogen, –OH, and C1-C4 alkyloxy, or wherein each of R^{11a} and R^{11b}, when present, together comprise =O; wherein R^{12}, when present, is hydrogen, C1-C4 alkyl, C3-C6 cycloalkyl, or –(C1-C4 alkyl)(C3-C6 cycloalkyl); wherein each of R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently selected from hydrogen, halogen, –CN, $–NH_2$, –OH, $–NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein R^2 is selected from $–(CH_2)_nCy^1$, $–O(CH_2)_nCy^1$, $–NR^{13}(CH_2)_nCy^1$, $–CH(OH)Cy^1$, and Cy^1; wherein n, when present, is 0, 1, or 2; wherein R^{13}, when present, is selected from hydrogen and C1-C4 alkyl; wherein Cy^1 is a C4-C9 cycloalkyl, a C3-C9 heterocycle having at least one O, S, or N atom, or a C2-C9 heteroaryl having at least one O, S, or N atom, and substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–NH_2$, –OH, $–NO_2$, =O, C3-C6 cycloalkyl, C2-C5 heterocycloalkyl, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-

[0013] Also provided are methods for making a disclosed compound.

[0014] Also provided are pharmaceutical compositions comprising a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

[0015] Also provided are methods of modulating PINK1 kinase activity in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount of at least one disclosed compound.

[0015a] In another aspect, there is provided the use of an effective amount of the compound as defined above in the manufacture of a medicament for modulating PINK1 kinase activity in a subject in need thereof.

[0016] Also disclosed are methods of modulating PINK1 kinase activity in at least one cell, the method comprising contacting the cell with an effective amount of at least one disclosed compound.

[0017] Also provided are methods for treating a disorder in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount of at least one disclosed compound, wherein the disorder is a neurodegenerative disorder, a mitochondrial disorder, a fibrosis, or cardiomyopathy.

[0017a] In another aspect, there is provided the use of the compound as defined above in the manufacture of a medicament for the treatment of a disorder in a subject in need thereof, wherein the disorder is a neurodegenerative disorder, a mitochondrial disorder, a fibrosis, or cardiomyopathy.

[0017b] In another aspect, there is provided a compound as defined above for use as a medicament.

[0018] Also provided are kits comprising a disclosed compound and one or more of: (a) at least one agent known for the treatment of a neurodegenerative disorder, a mitochondrial disorder, a fibrosis, and cardiomyopathy; (b) instructions for administering the compound in connection with the neurodegenerative disorder, a mitochondrial disorder, a fibrosis, or cardiomyopathy; and/or (c) instructions for treating the disorder.

[0019] Still other objects and advantages of the present disclosure will become readily apparent by those skilled in the art from the following detailed description, wherein it is shown and described only the preferred embodiments, simply by way of illustration of the best mode. As will be realized, the disclosure is capable of other and different embodiments,

and its several details are capable of modifications in various obvious respects, without departing from the disclosure. Accordingly, the description is to be regarded as illustrative in nature and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

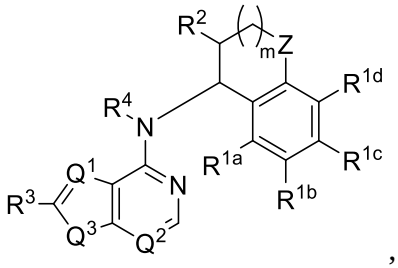
[0020] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several embodiments and together with the description serve to explain the principles of the invention.

[0021] FIG. 1A-F show representative data demonstrating the potency and toxicity of the compounds nos. EP-0035985, EP-0037821, EP-0038098, and EP-0038099 in the presence of

CLAIMS

What is claimed is:

1. A compound having a structure represented by a formula:



,

wherein m is 0 or 1;

wherein each of Q^1 and Q^2 is independently N or CH;

wherein Q^3 is CH_2 or NH;

wherein Z is $CR^{11a}R^{11b}$, NR^{12}, or O;

wherein each of R^{11a} and R^{11b}, when present, is independently selected from hydrogen, halogen, –OH, and C1-C4 alkyloxy,

or wherein each of R^{11a} and R^{11b}, when present, together comprise =O;

wherein R^{12}, when present, is hydrogen, C1-C4 alkyl, C3-C6 cycloalkyl, or –(C1-C4 alkyl)(C3-C6 cycloalkyl);

wherein each of R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently selected from hydrogen, halogen, –CN, $–NH_2$, –OH, $–NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino;

wherein R^2 is selected from $–(CH_2)_nCy^1$, $–O(CH_2)_nCy^1$, $–NR^{13}(CH_2)_nCy^1$, $–CH(OH)Cy^1$, and Cy^1;

wherein n, when present, is 0, 1, or 2;

wherein R^{13}, when present, is selected from hydrogen and C1-C4 alkyl;

wherein Cy^1 is a C4-C9 cycloalkyl, a C3-C9 heterocycle having at least one O, S, or N atom, or a C2-C9 heteroaryl having at least one O, S, or N atom, and substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–NH_2$, –OH, $–NO_2$, =O, C3-C6 cycloalkyl, C2-C5 heterocycloalkyl, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, –(C1-C4)–O–(C1-C4 alkyl), –C(O)(C1-C4 alkyl), $–S(O)R^{14}$, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino;

wherein R^{14}, when present, is selected from –OH, $–NH_2$, –O(C1-C4 alkyl), –NH(C1-C4 alkyl), and –N(C1-C4 alkyl)(C1-C4 alkyl);

wherein R^3 is a 3- to 6-membered cycloalkyl, a C1-C6 haloalkyl, C1-C6 haloalkoxy, or C1-C6 halohydroxyalkyl; and

wherein R^4 is selected from hydrogen and C1-C4 alkyl,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R^2 is selected from $–O(CH_2)_nCy^1$, $–NR_{13}(CH_2)_nCy^1$, and Cy^1; Cy^1 is a C3-C9 heterocycle having at least one O, S, or N atom, and substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–NH_2$, –OH, $–NO_2$, =O, C3-C6 cycloalkyl, C2-C5 heterocycloalkyl, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; and R^4 is hydrogen.

3. The compound of claim 1, wherein m is 1.

4. The compound of claim 1, wherein Q^1 is CH.

5. The compound of claim 1, wherein Q^2 is N.

6. The compound of claim 1, wherein Q^3 is NH.

7. The compound of claim 1, wherein Q^1 is CH, Q^2 is N, and Q^3 is NH.

8. The compound of claim 1, wherein Z is CH_2.

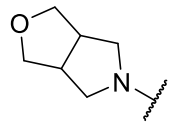
9. The compound of claim 1, wherein each of R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently hydrogen, halogen, or C1-C4 alkyl.

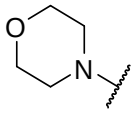
10. The compound of claim 1, wherein R^2 is selected from $–O(CH_2)_nCy^1$, $–NR^{13}(CH_2)_nCy^1$, $–CH(OH)Cy^1$, and Cy^1;

11. The compound of claim 1, wherein R^2 is Cy^1.

12. The compound of claim 11, wherein Cy^1 is a C3-C9 heterocycle having at least one O, S, or N atom and unsubstituted.

13. The compound of claim 11, wherein Cy^1 is a structure represented by a formula selected from:



and 

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14. The compound of claim 1, wherein Cy^1 is a C3-C9 heterocycle having at least one O, S, or N atom.

15. The compound of claim 14, wherein the C3-C9 heterocycle is a monocyclic heterocycle.

16. The compound of claim 14, wherein the C3-C9 heterocycle is a bicyclic heterocycle.

17. The compound of claim 14, wherein the C3-C9 heterocycle is a spirocyclic heterocycle.

18. The compound of claim 14, wherein the C3-C9 heterocycle is a fused heterocycle.

19. The compound of claim 1, wherein Cy^1 is a C2-C9 heteroaryl having at least one O, S, or N atom.

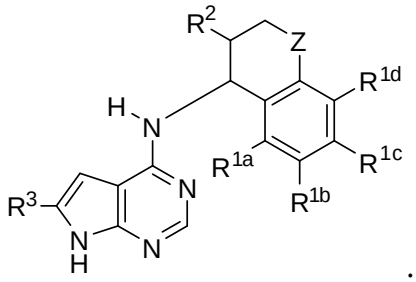
20. The compound of claim 1, wherein Cy^1 is a C3-C9 heterocycle having at least one O, S, or N atom, and substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–NH_2$, –OH, $–NO_2$, =O, C3-C6 cycloalkyl, C2-C5 heterocycloalkyl, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino.

21. The compound of claim 1, wherein R^3 is a 3- to 6-membered cycloalkyl or a C1-C6 haloalkyl.

22. The compound of claim 1, wherein R^3 is a 3-membered cycloalkyl or $–CF_3$.

23. The compound of claim 1, wherein R^4 is hydrogen.

24. The compound of claim 1, wherein the compound has a structure represented by a formula:



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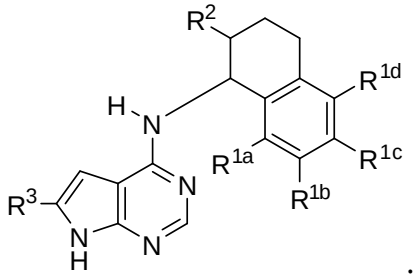
25. The compound of claim 1, wherein the compound has a structure represented by a formula:



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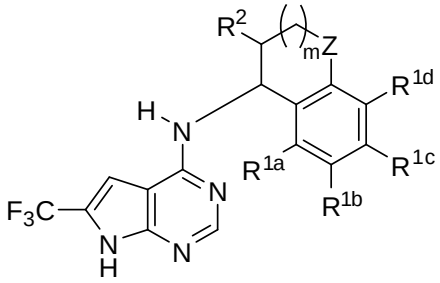
26. The compound of claim 1, wherein the compound has a structure represented by a formula selected from:



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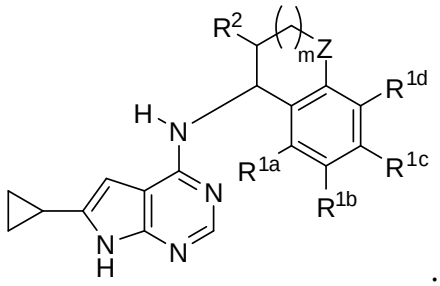

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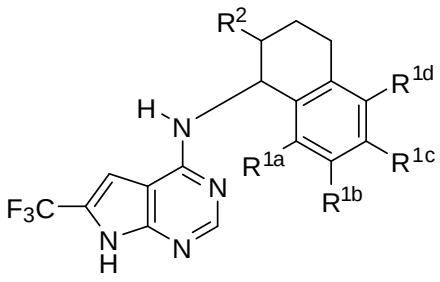
27. The compound of claim 1, wherein the compound has a structure represented by a formula selected from:



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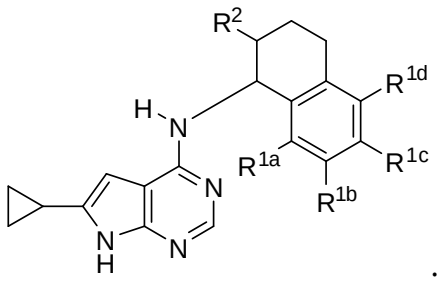

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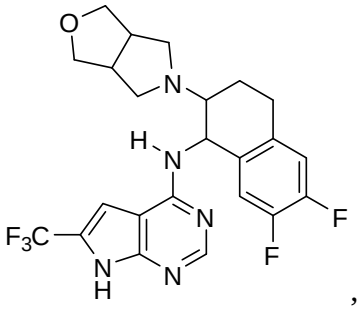
28. The compound of claim 1, wherein the compound is selected from: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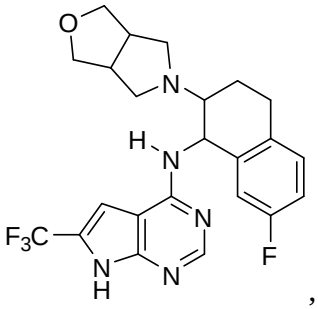
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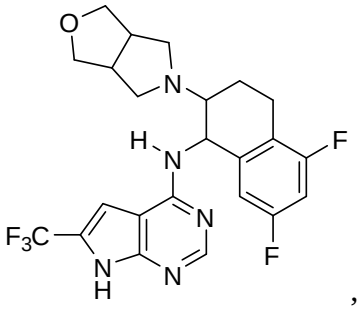
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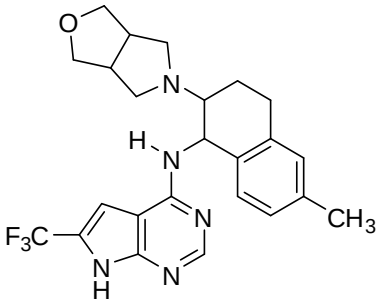
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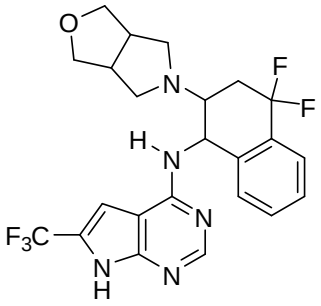
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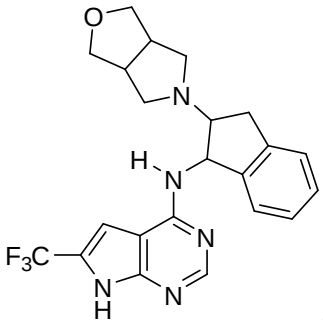
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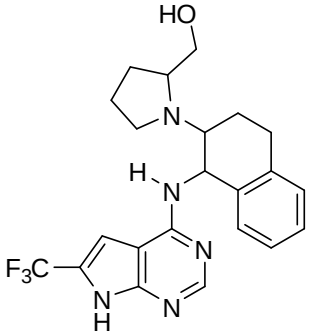
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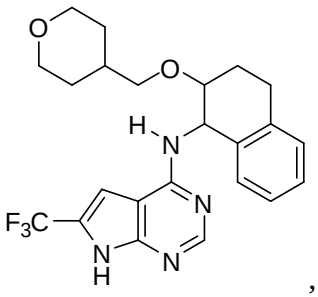
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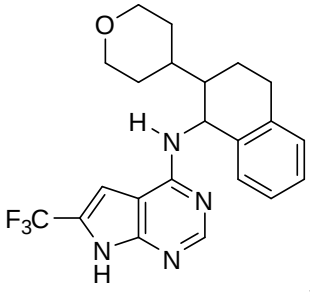
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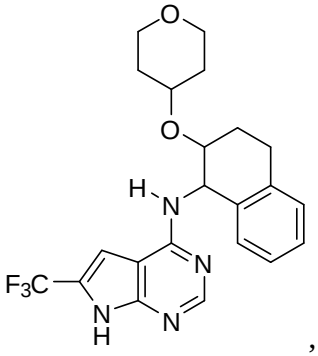
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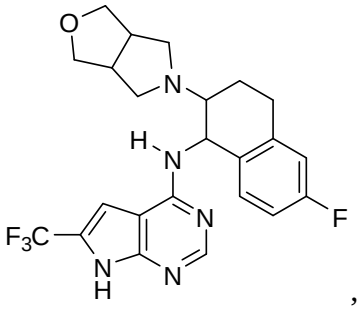
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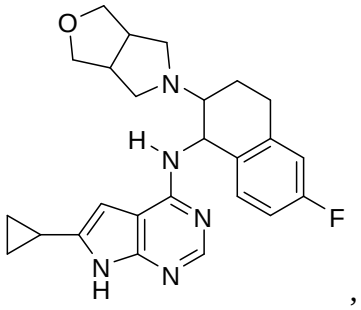
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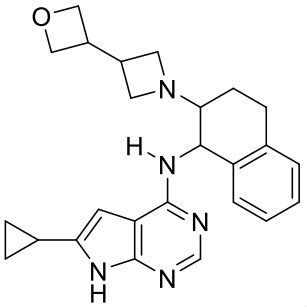
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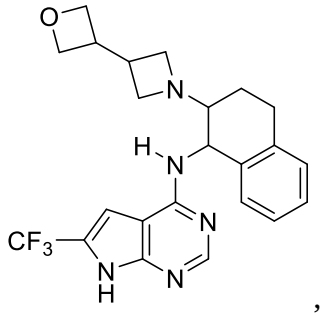
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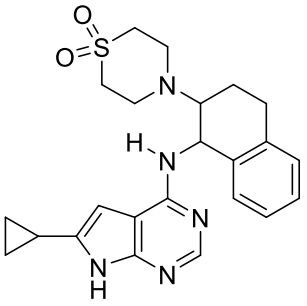
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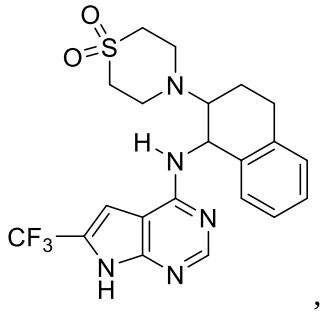
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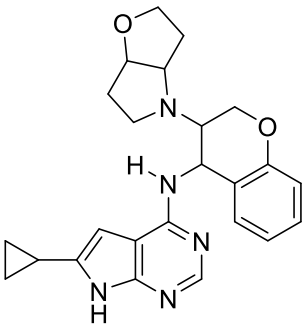
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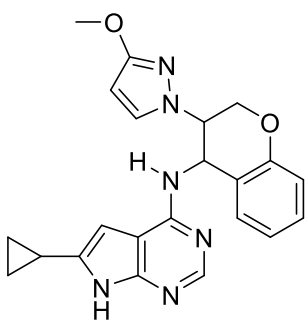
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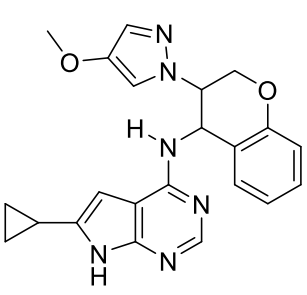
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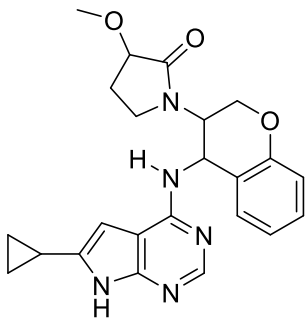
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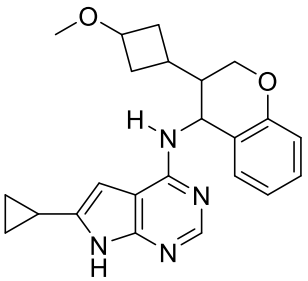
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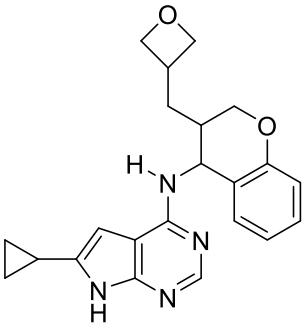
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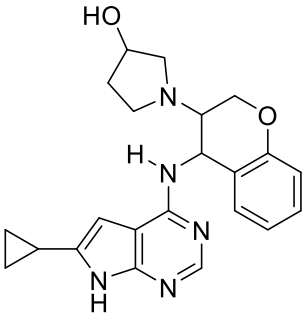
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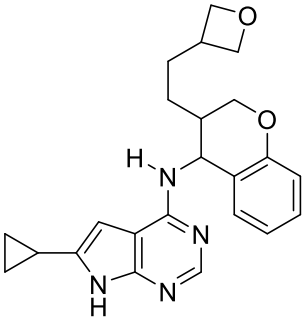
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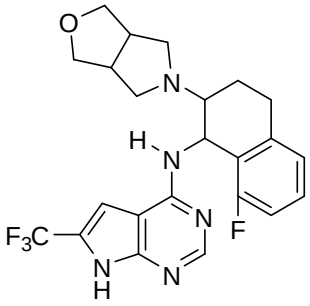
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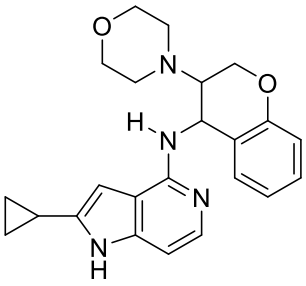
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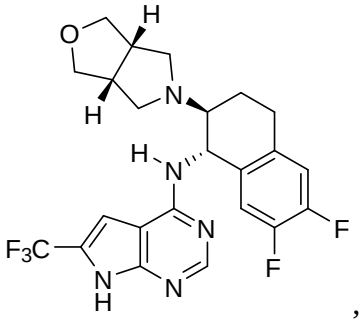
29. The compound of claim 1, wherein the compound is selected from: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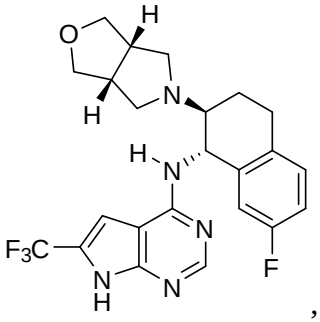
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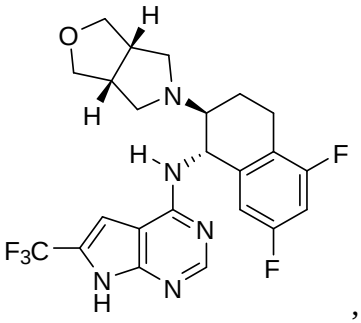
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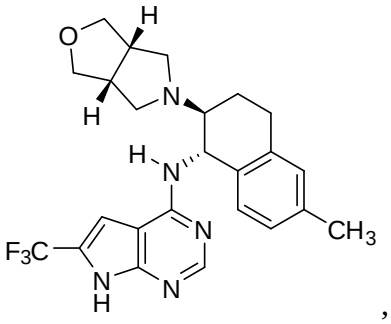
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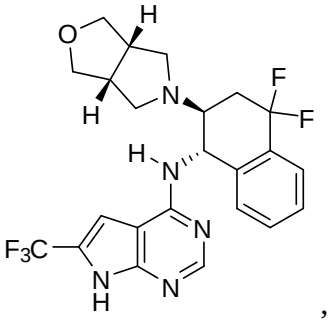
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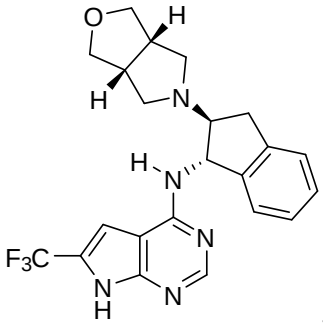
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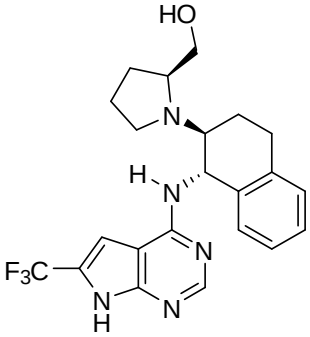
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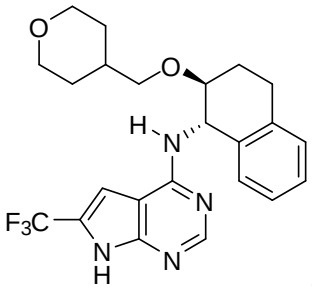
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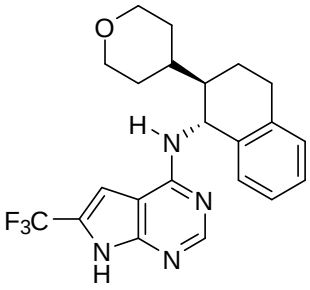
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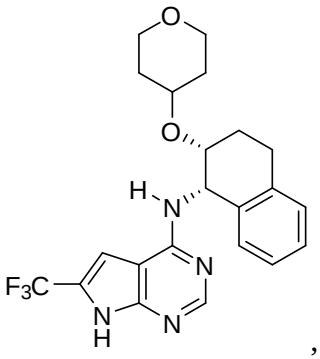
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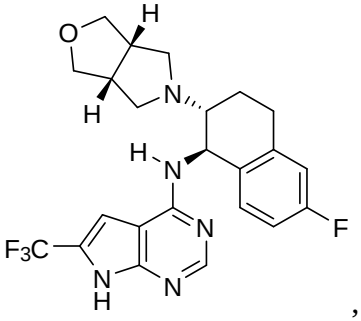
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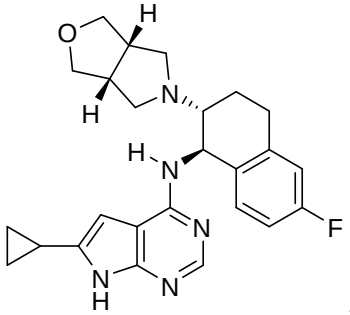
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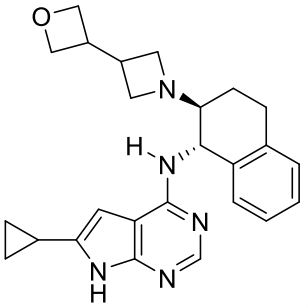
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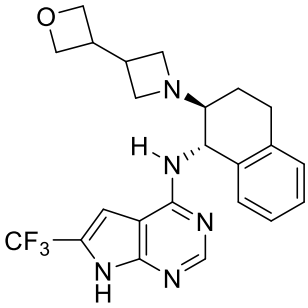
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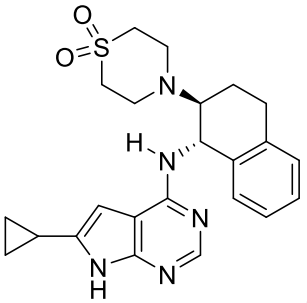
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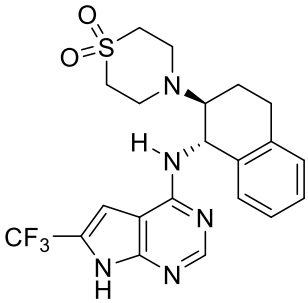
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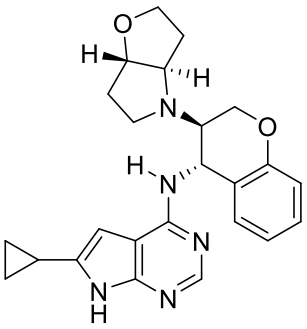
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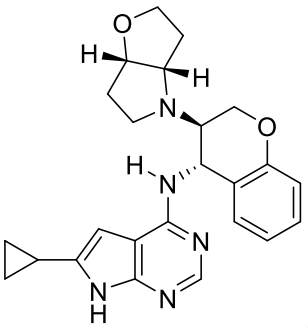
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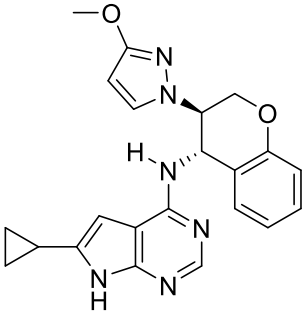
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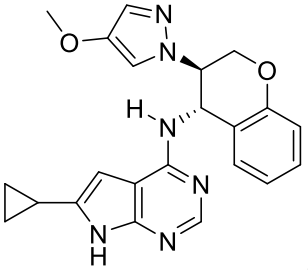
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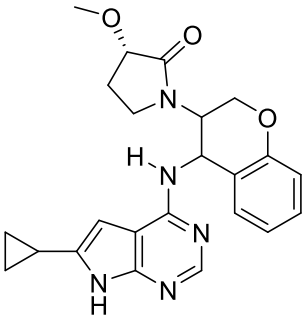
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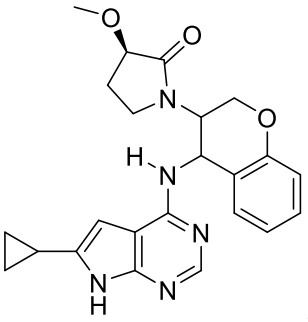
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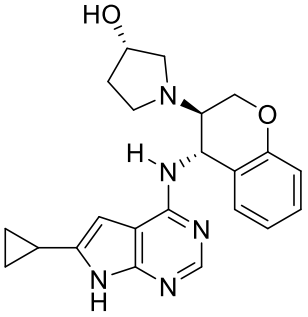
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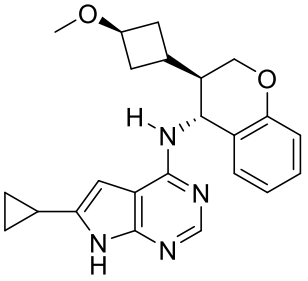
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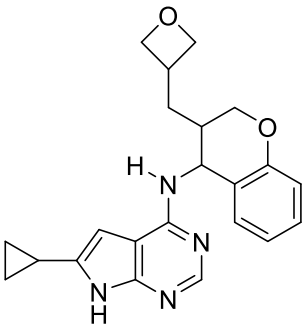
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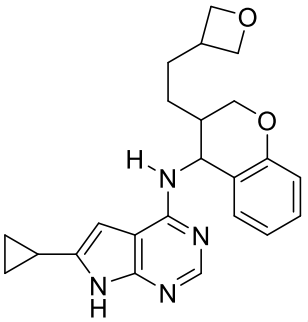
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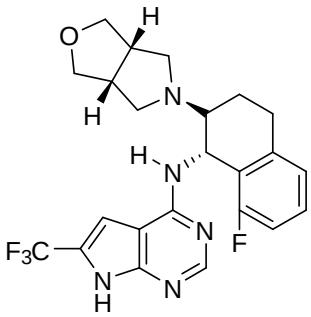
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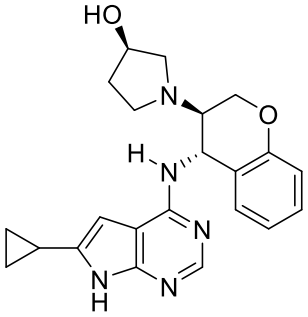
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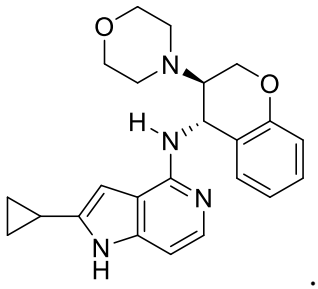
and  .

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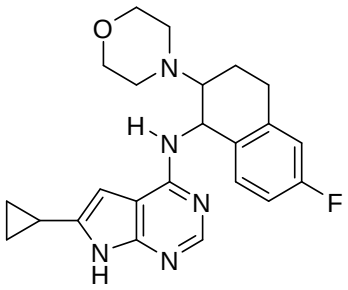
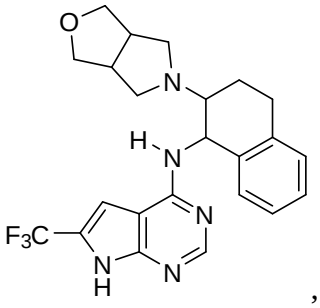
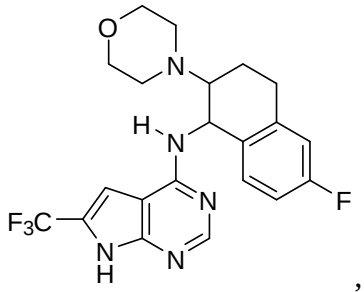
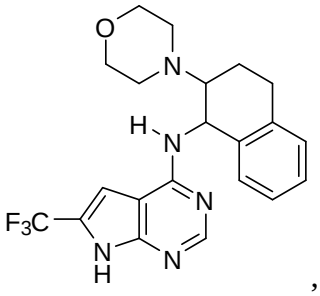
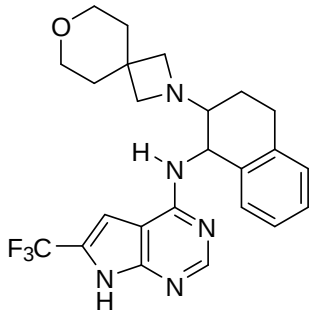
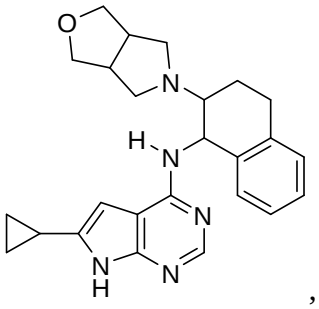
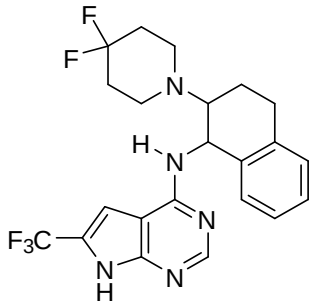
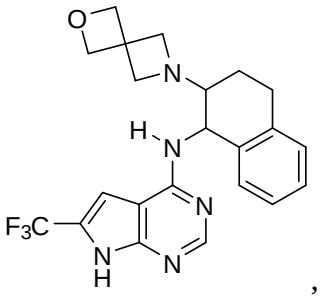
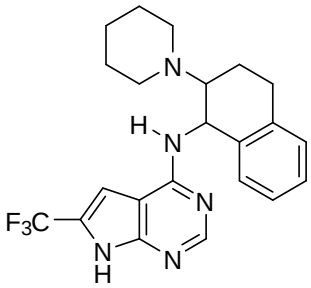
 ,  ,

 ,  ,

 ,  ,

 ,  ,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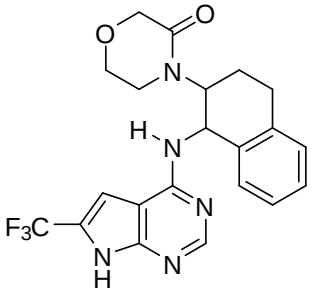
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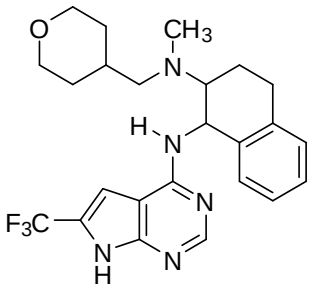
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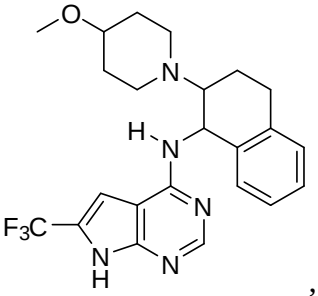
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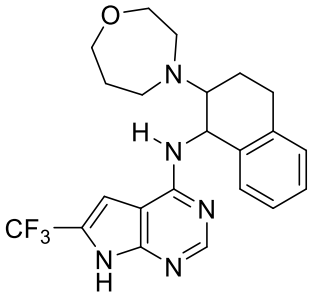
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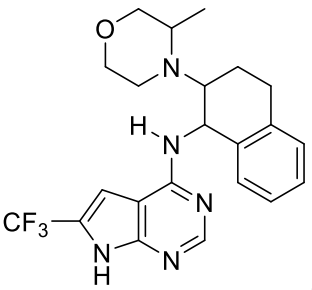
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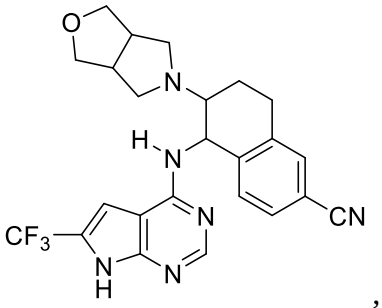
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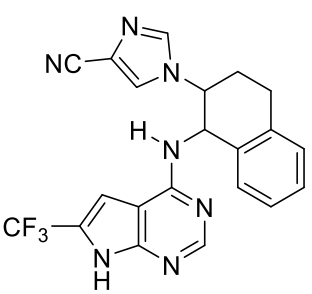
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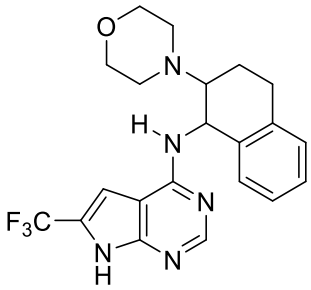
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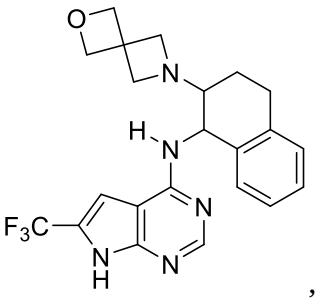
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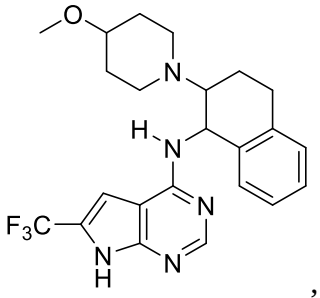
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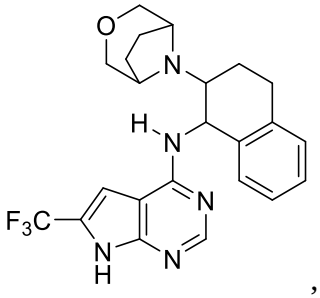
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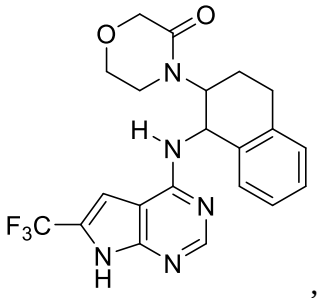
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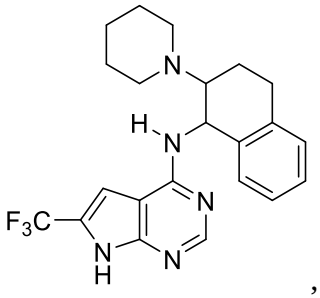
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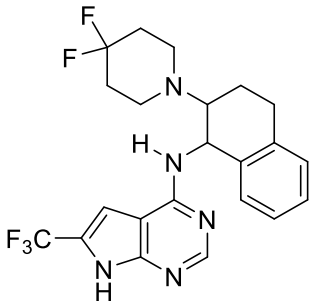
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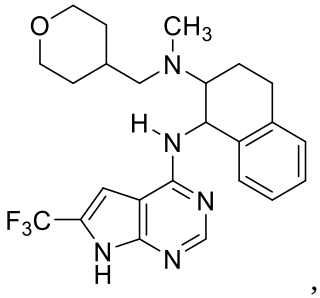
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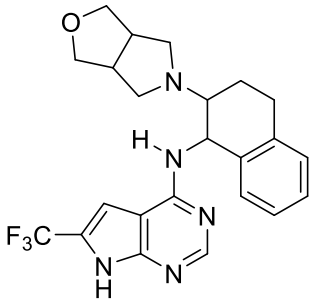
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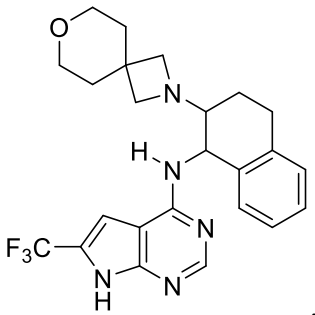
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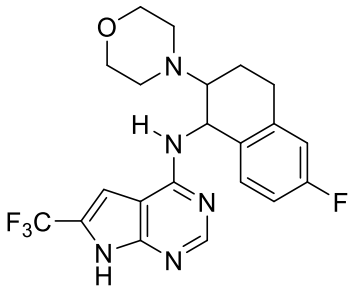
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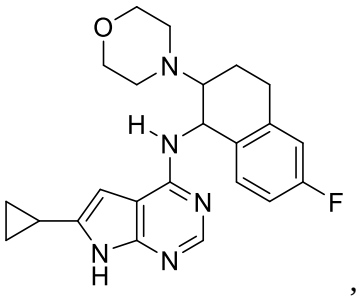
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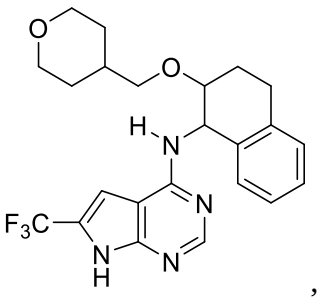
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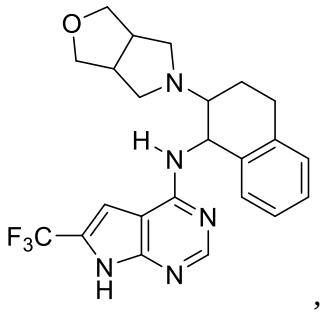
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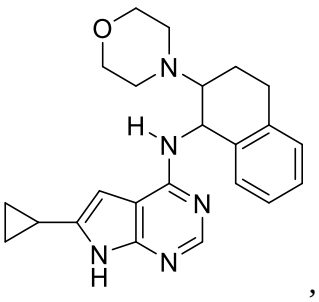
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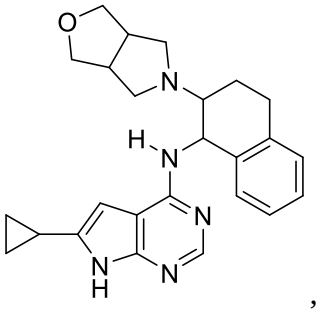
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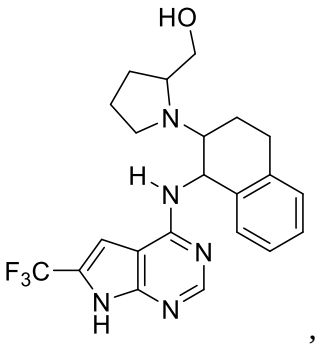
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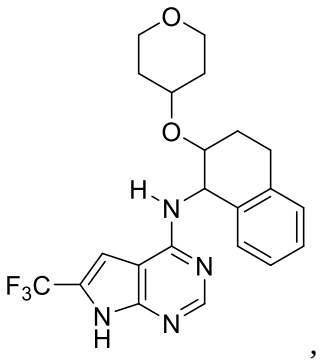
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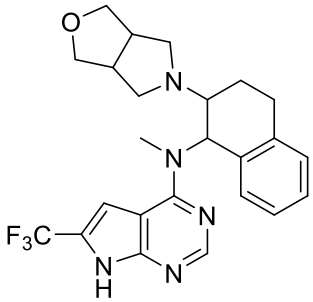
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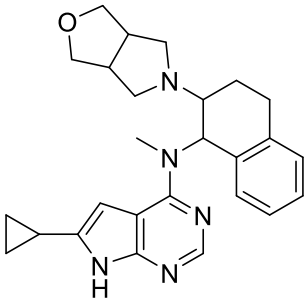
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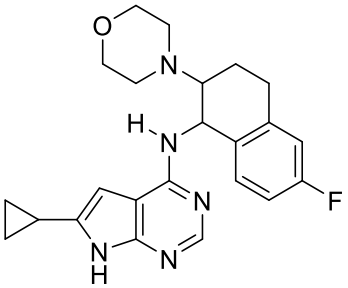
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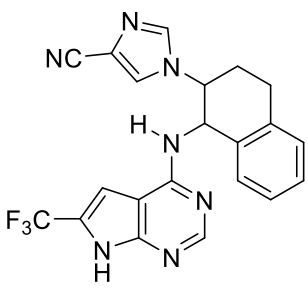
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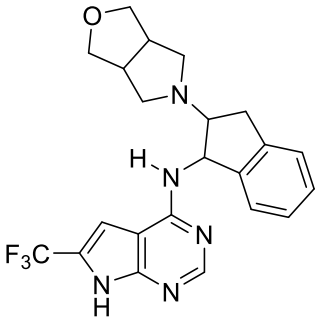
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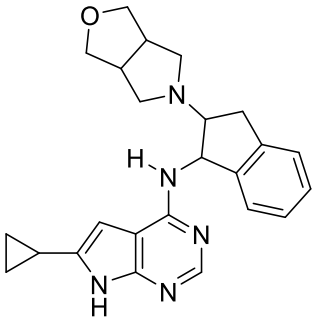
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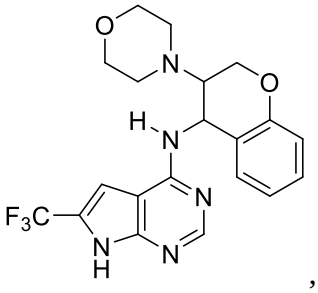
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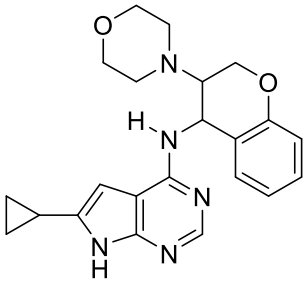
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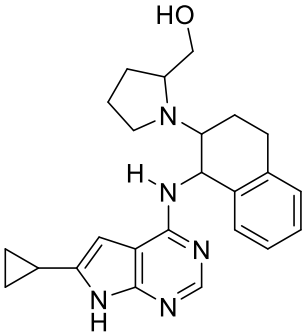
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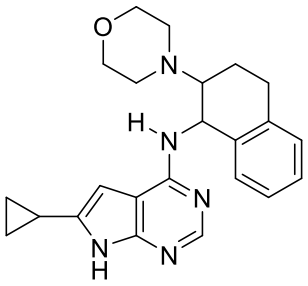
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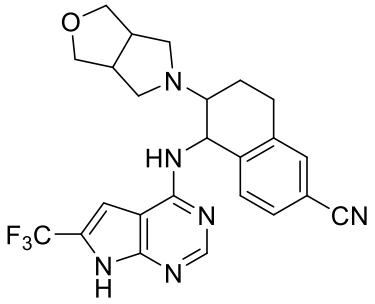
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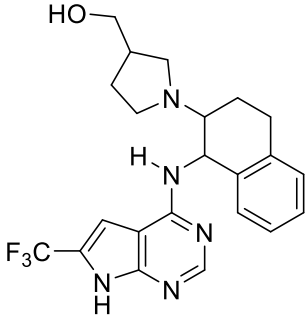
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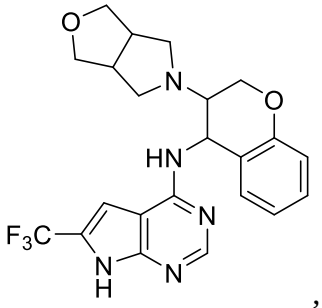
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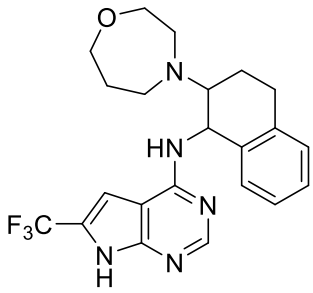
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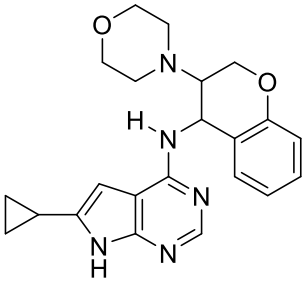
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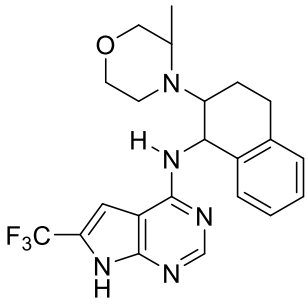
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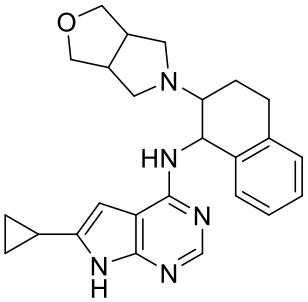
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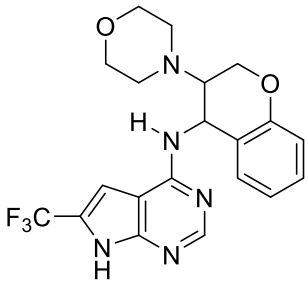
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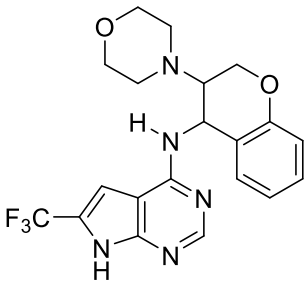
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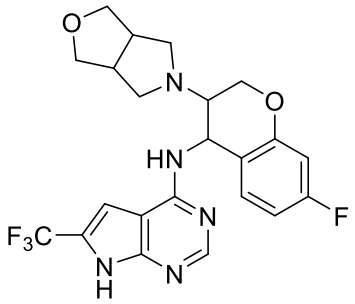
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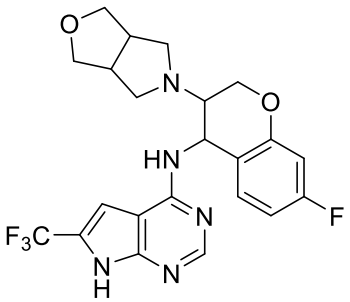
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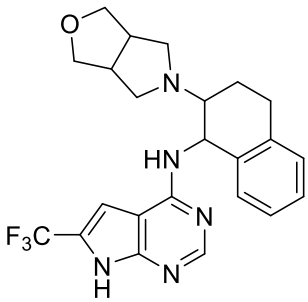
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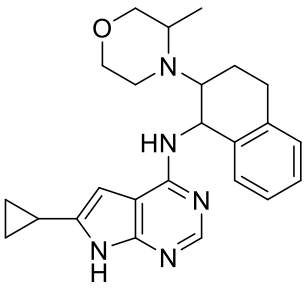
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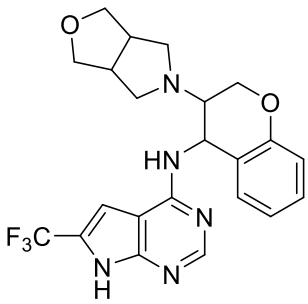
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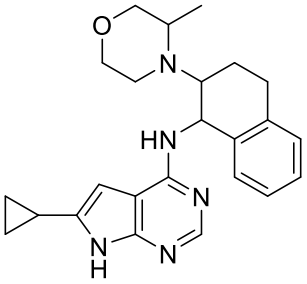
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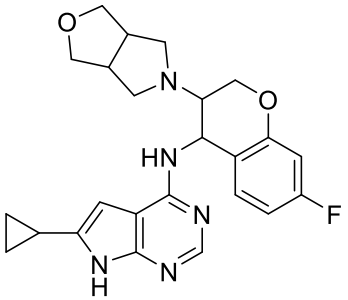
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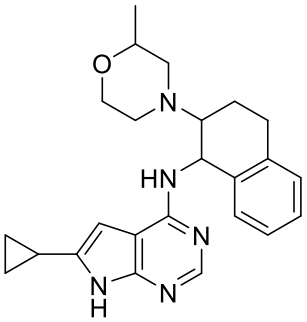
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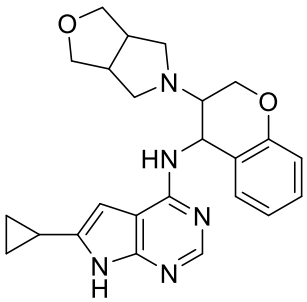
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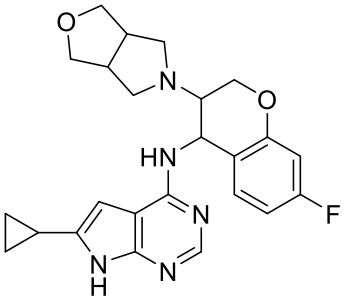
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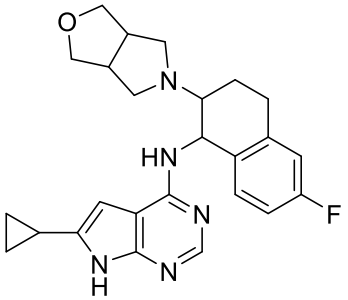
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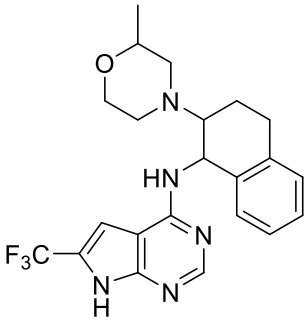
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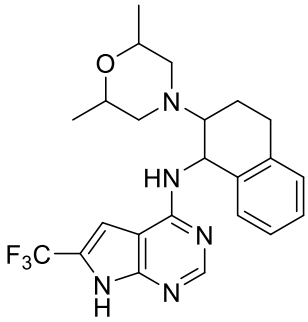
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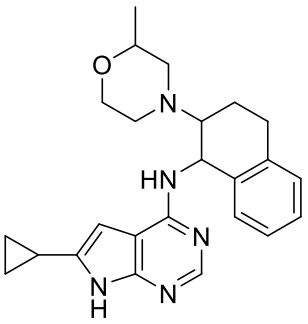
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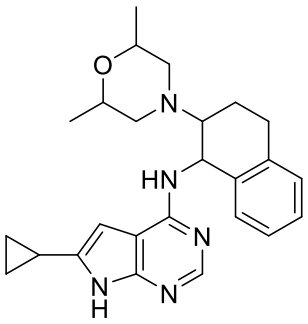
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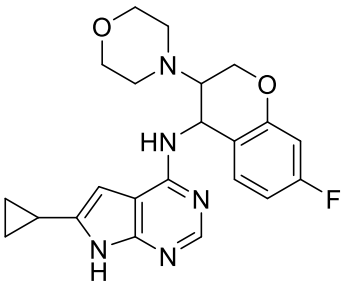
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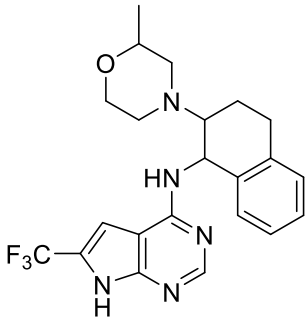
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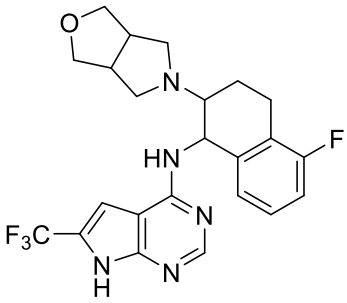
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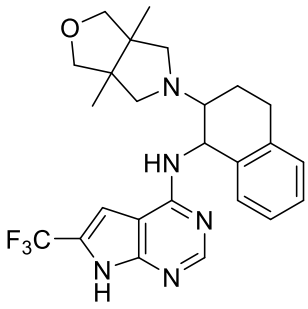
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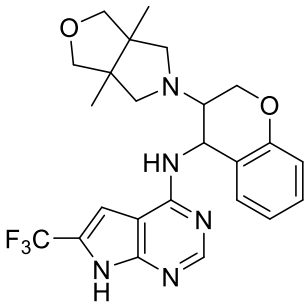
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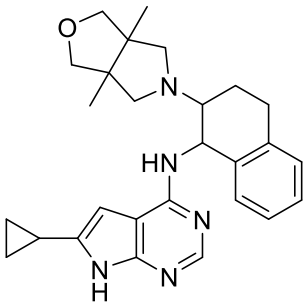
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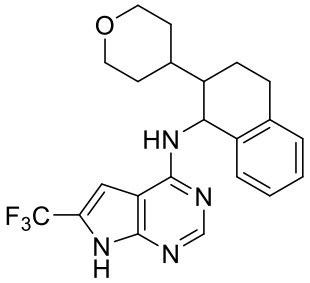
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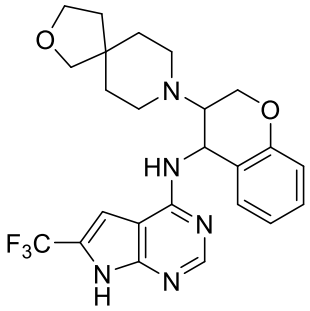
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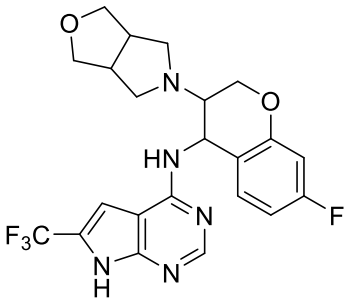
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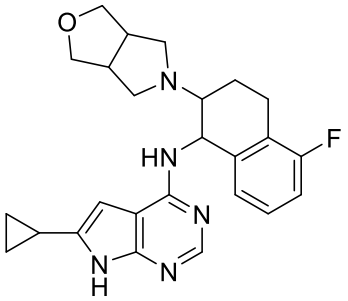
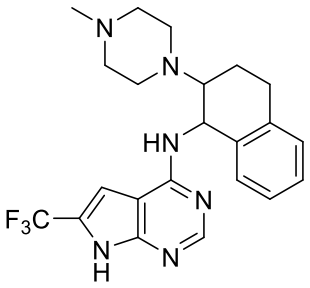
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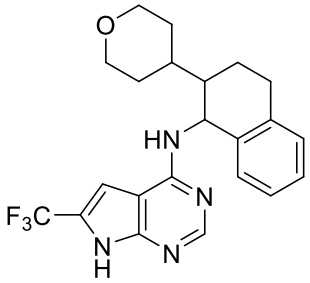
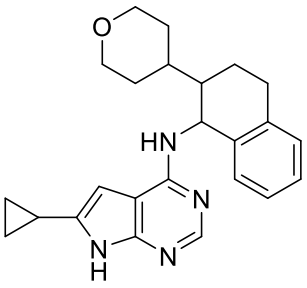
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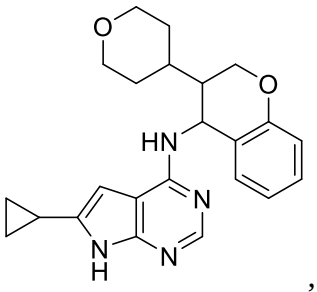

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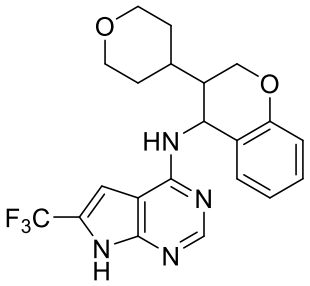
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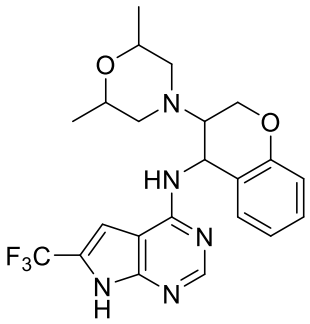
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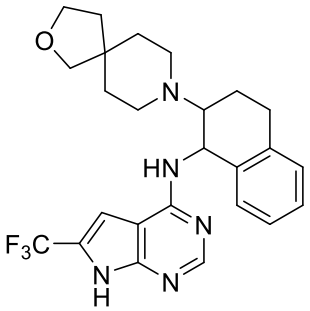
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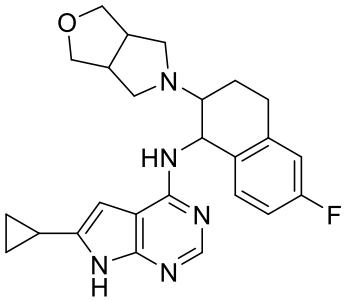
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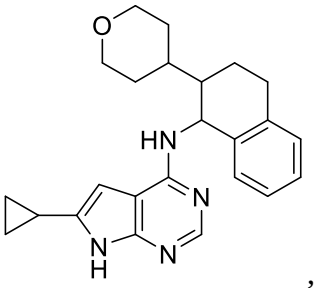
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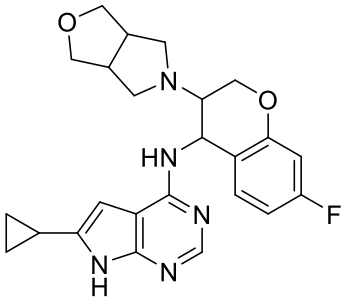
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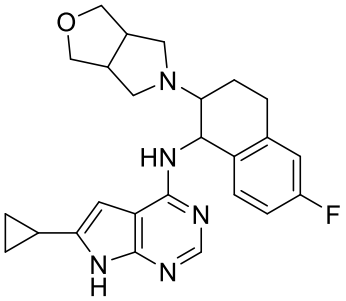
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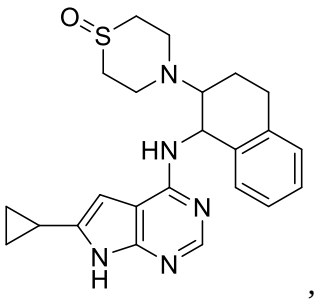
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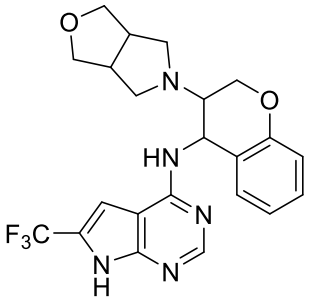
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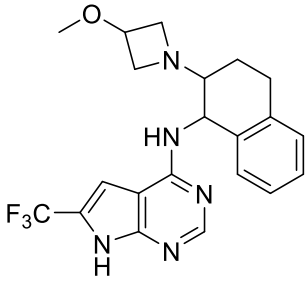
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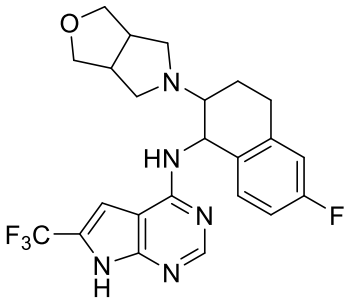
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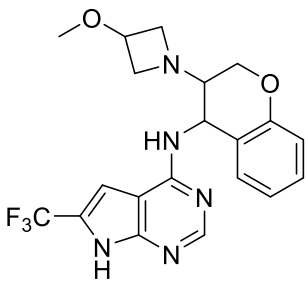
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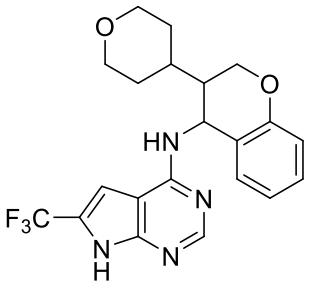
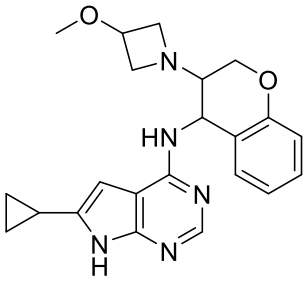
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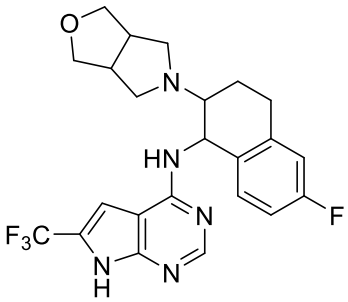
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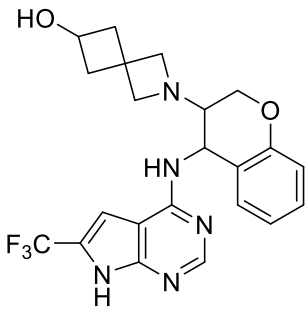
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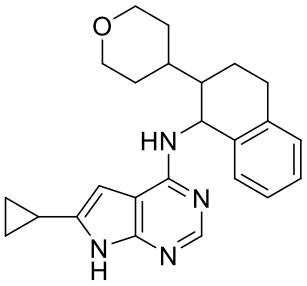
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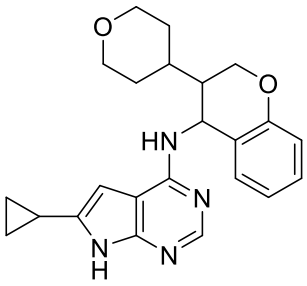
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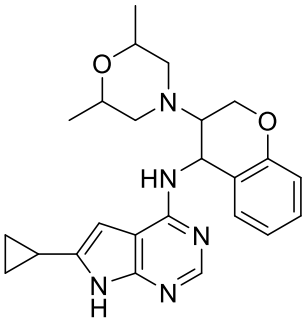
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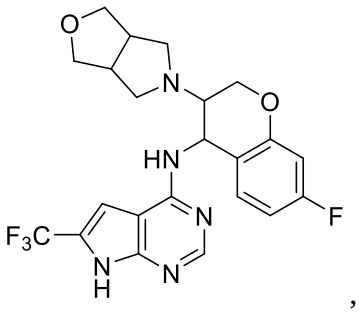
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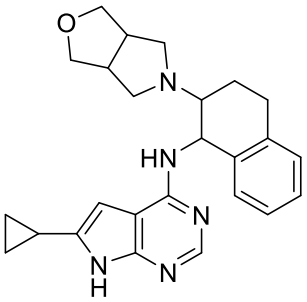
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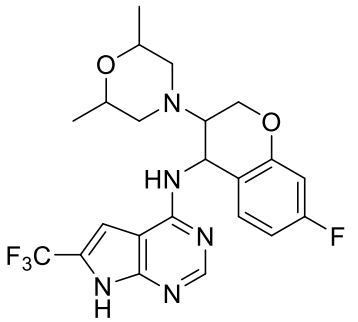
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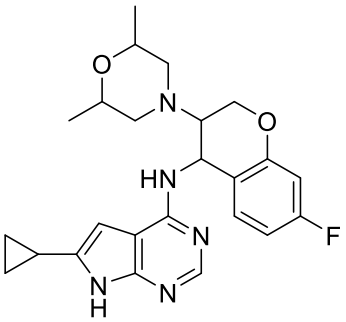
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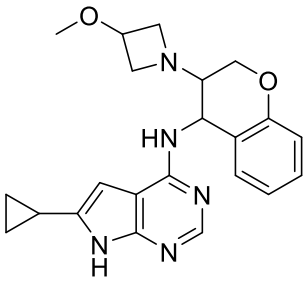
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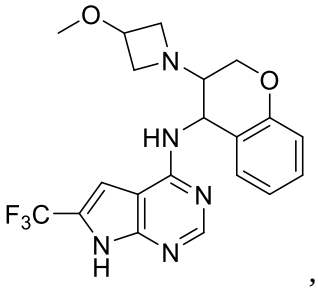
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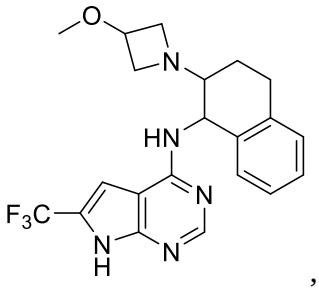
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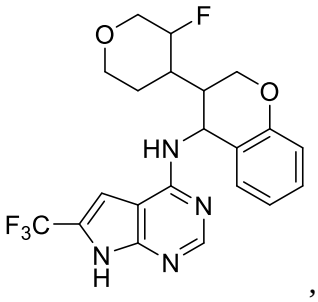
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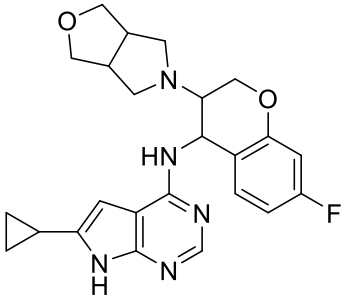

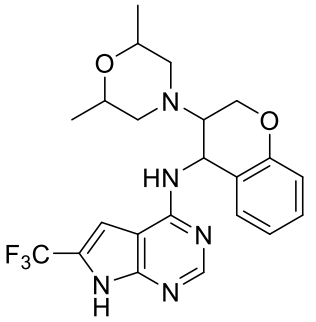

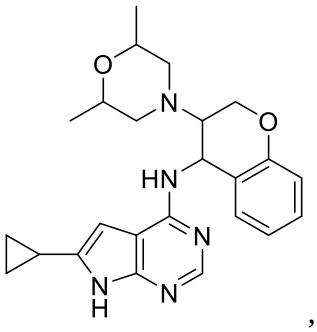
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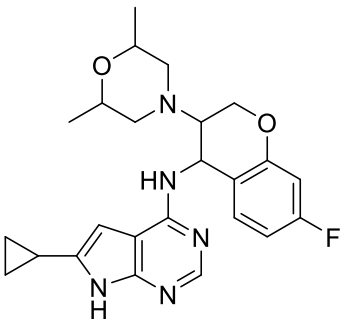

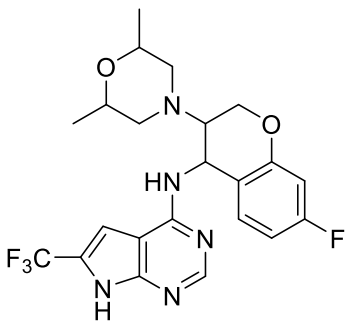
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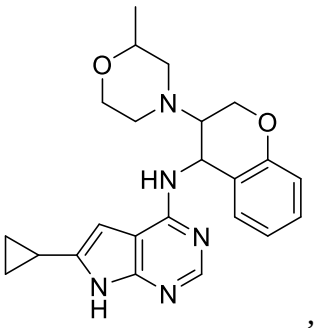
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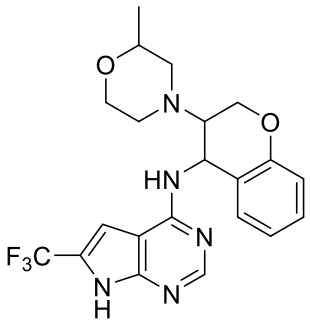
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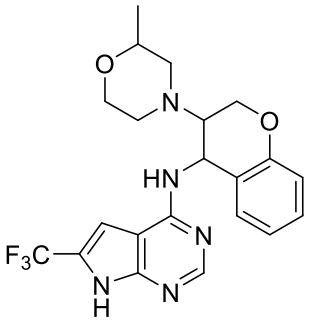
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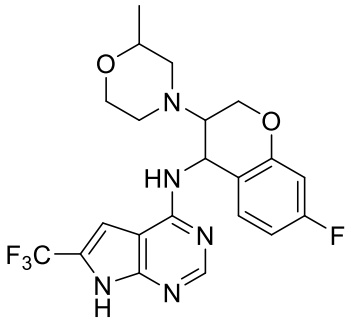
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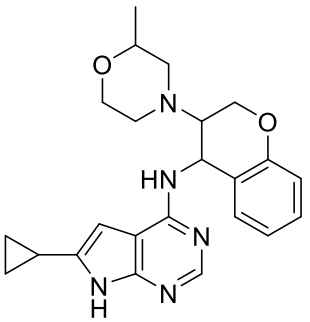
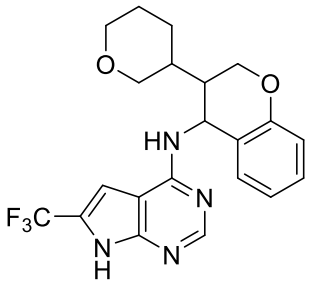
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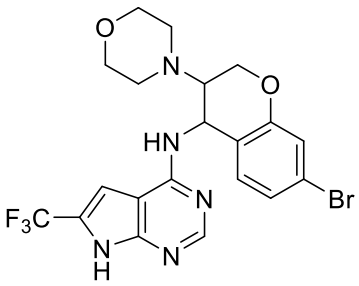
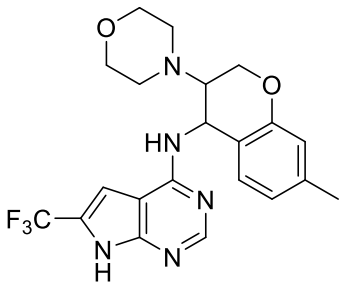
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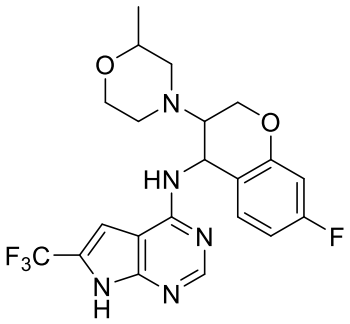
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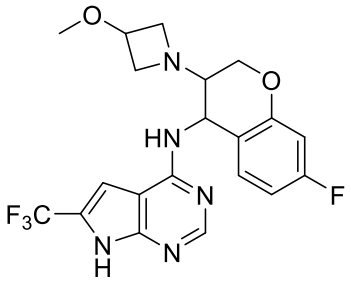
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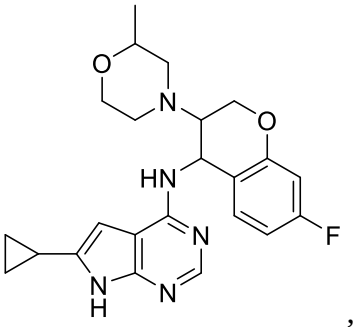
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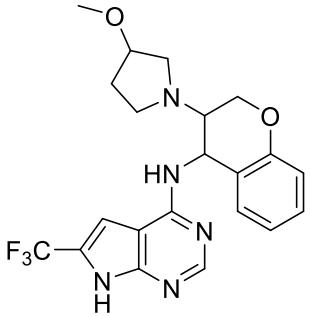
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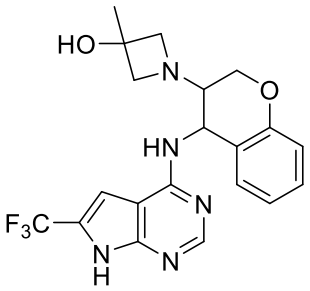
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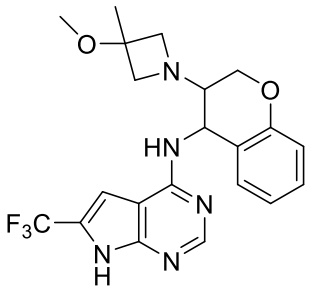
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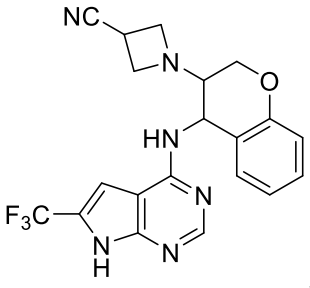
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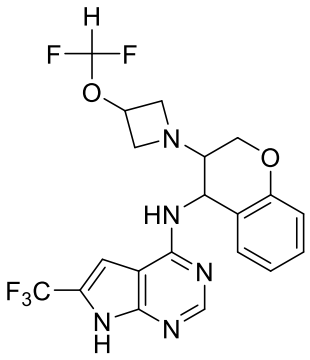
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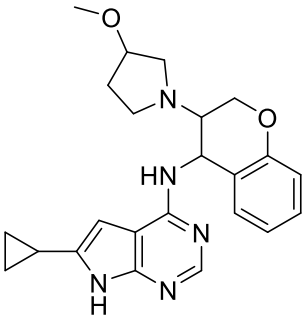
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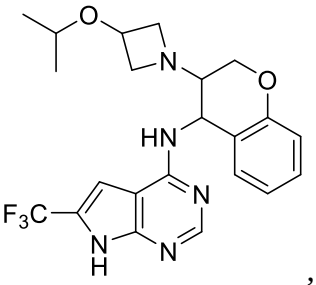
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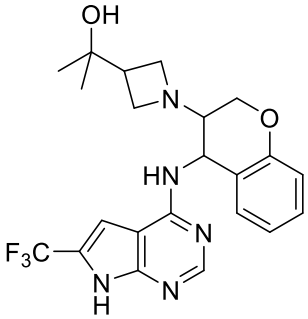
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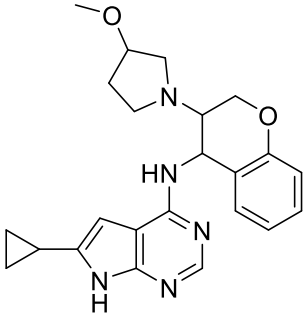
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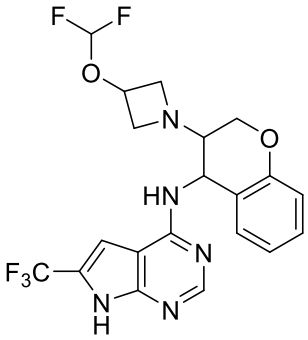
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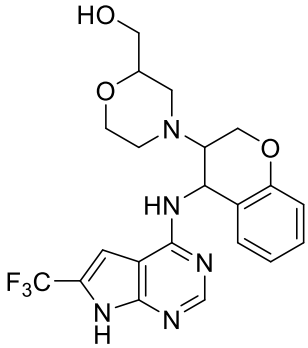
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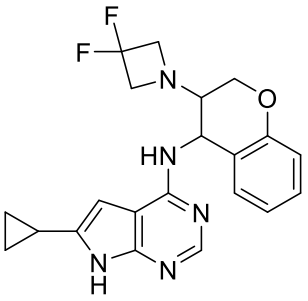
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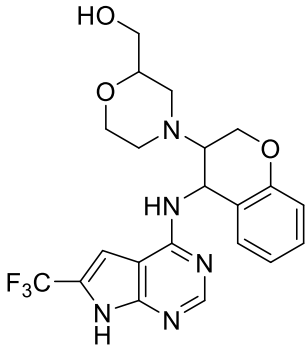
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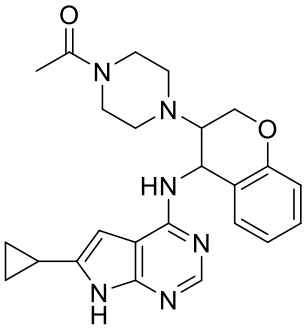
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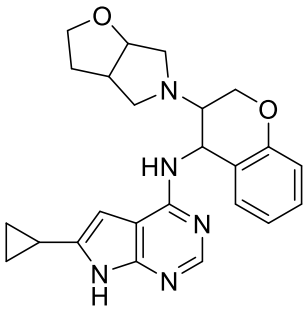
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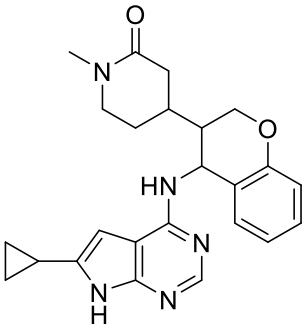
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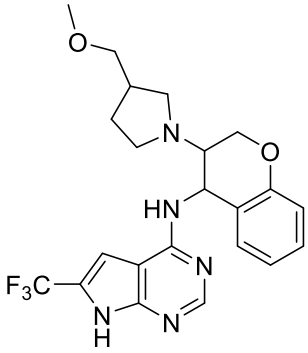
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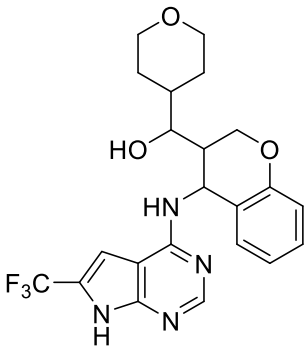
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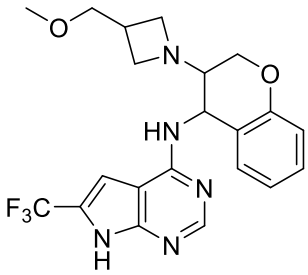
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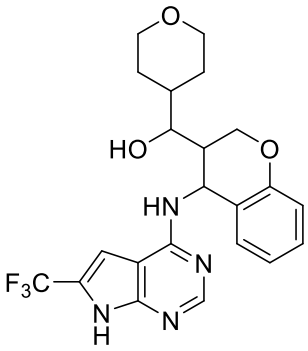
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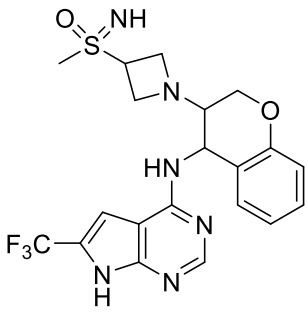
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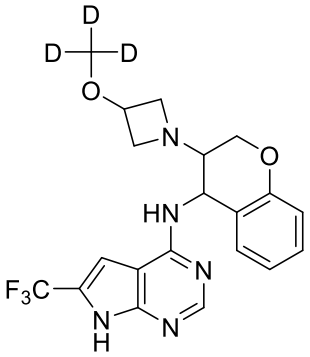
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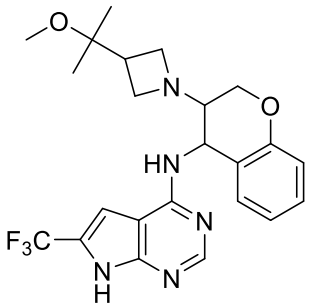
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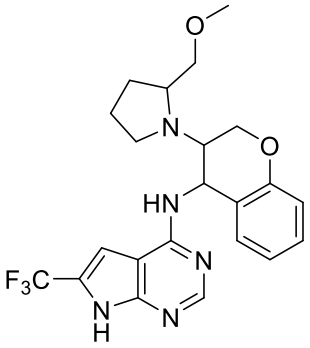
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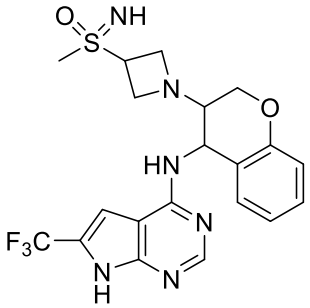
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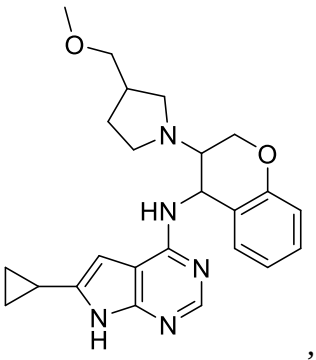
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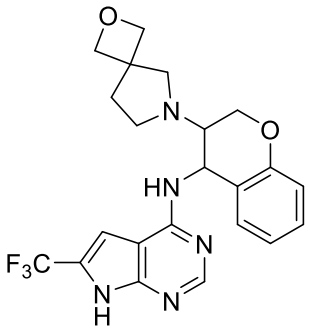
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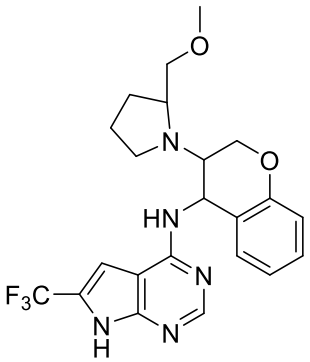
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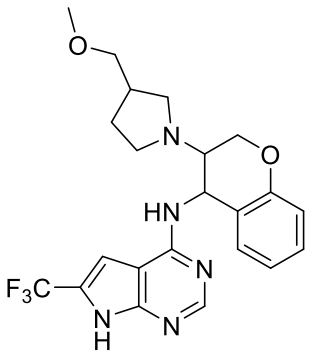
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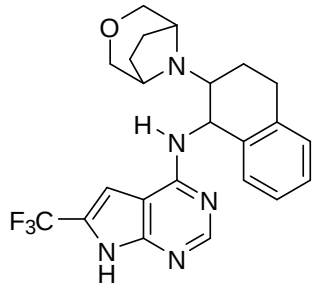
and  .

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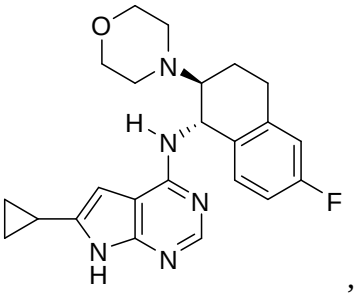
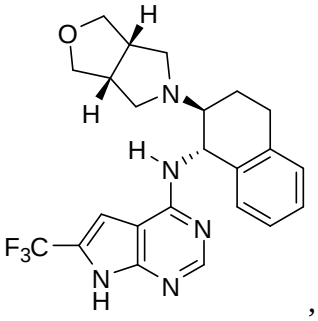
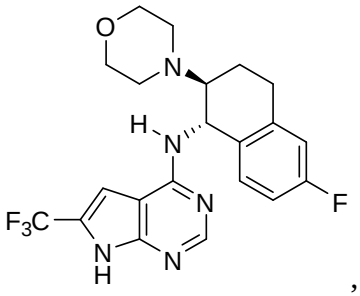
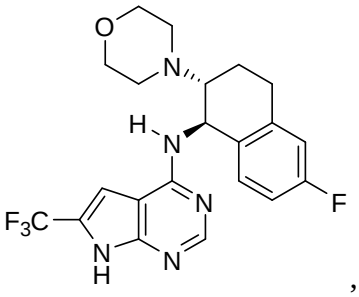
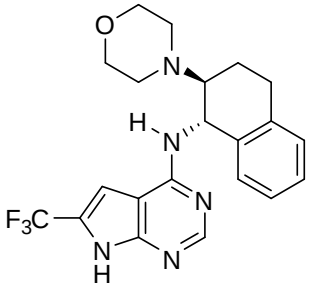
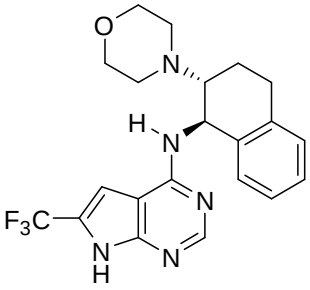
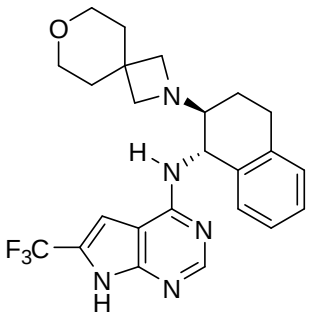
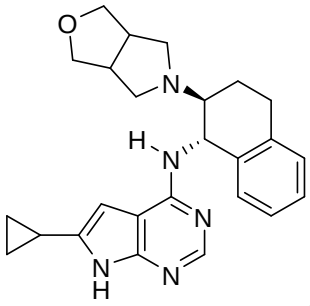
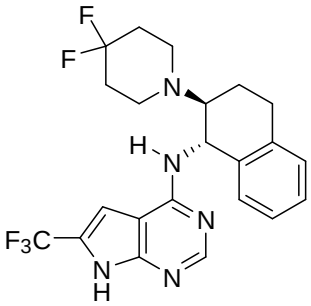
 ,  ,

 ,  ,

 ,  ,

 ,  ,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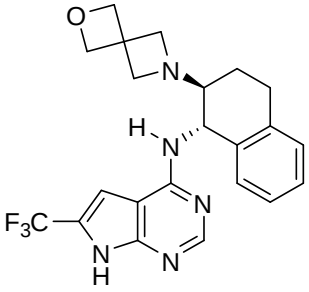
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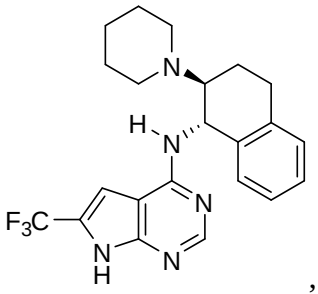
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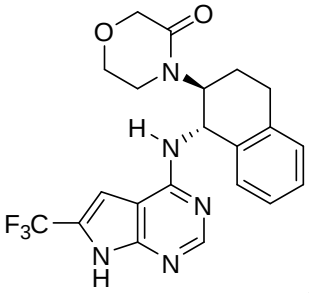
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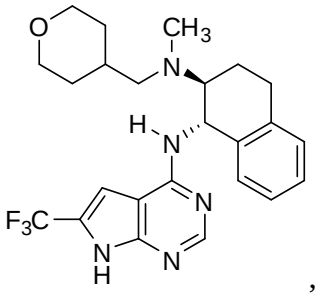
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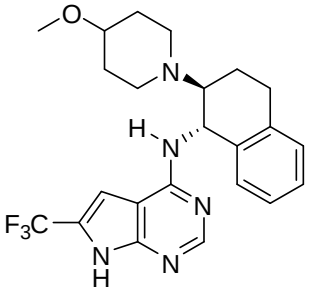
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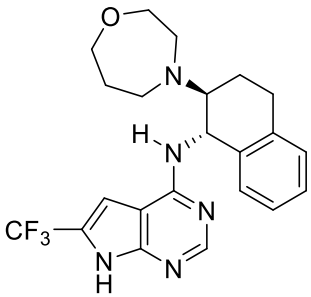
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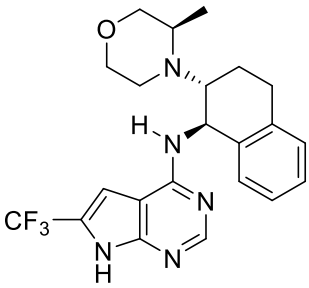
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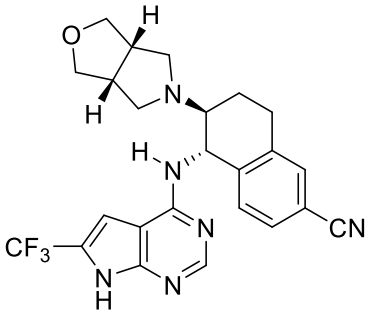
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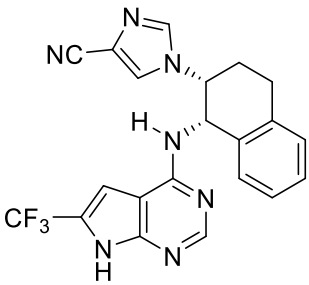
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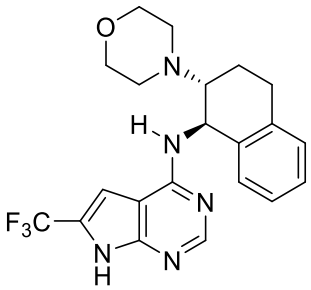
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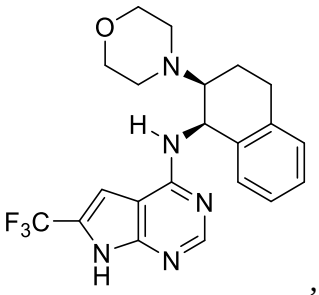
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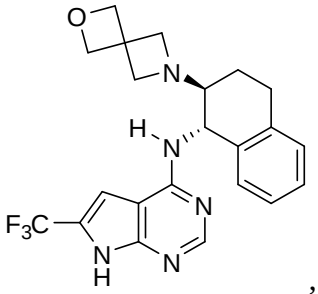
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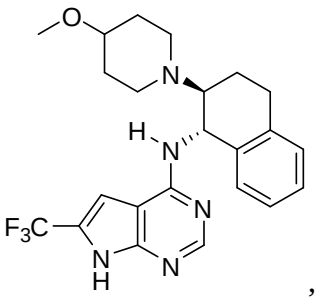
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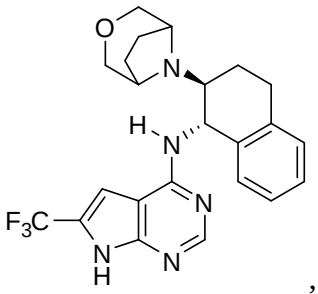
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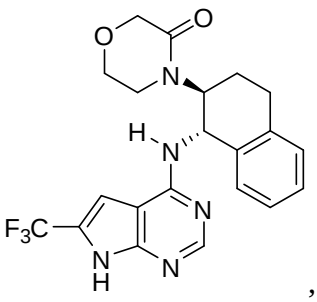
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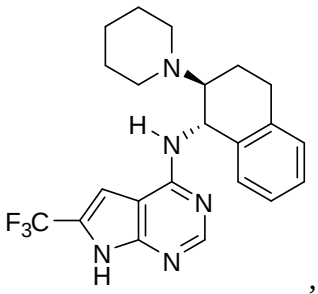
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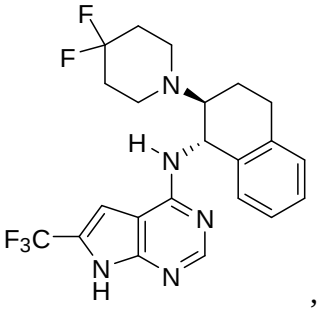
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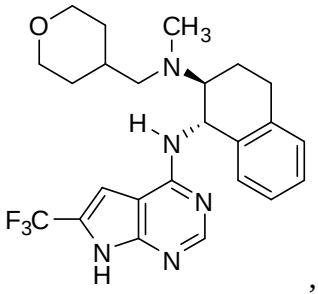
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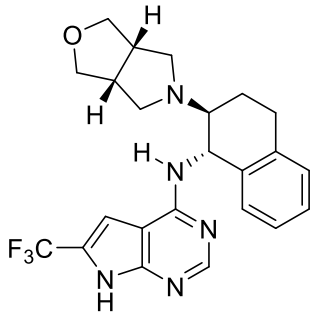
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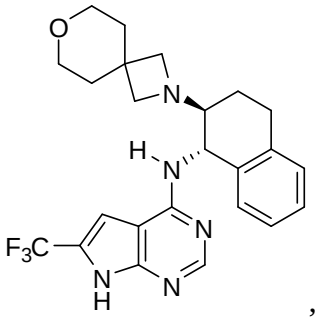
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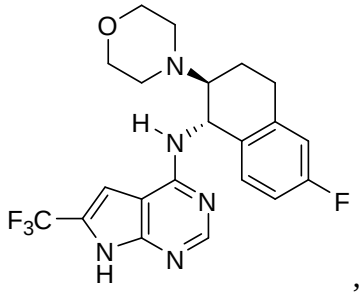
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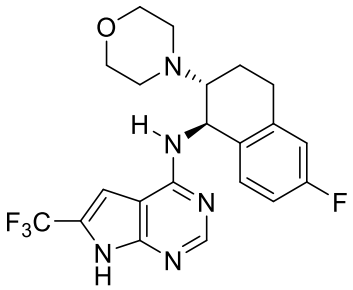
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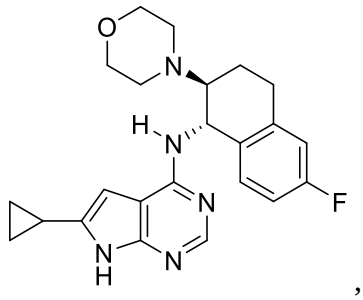
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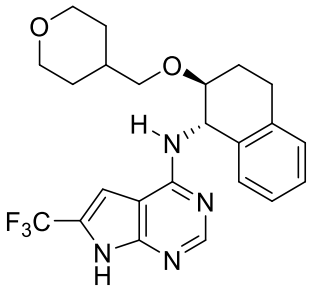
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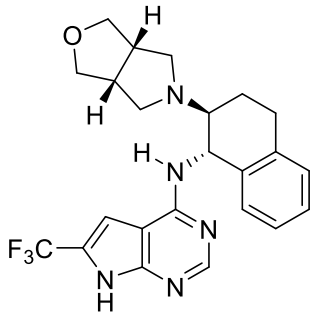
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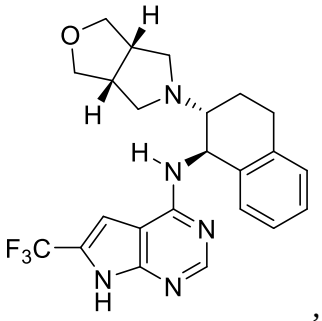
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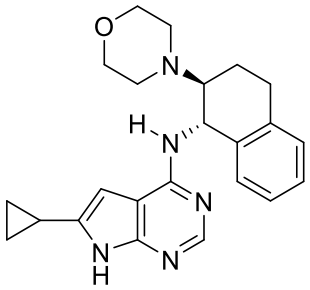
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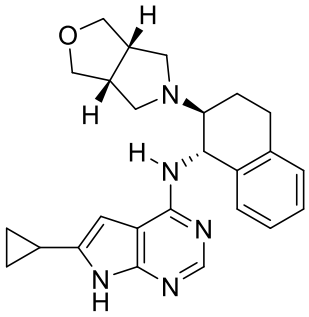
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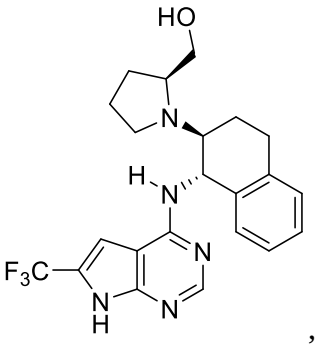
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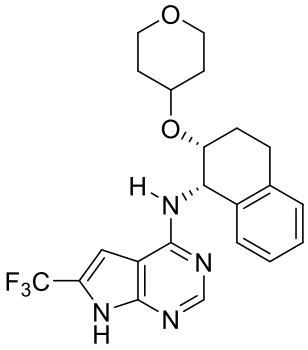
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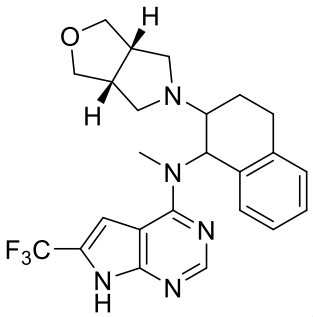
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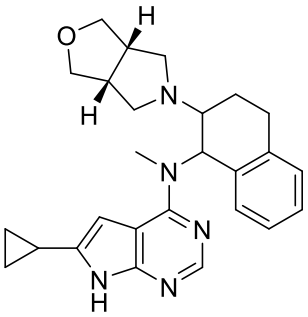
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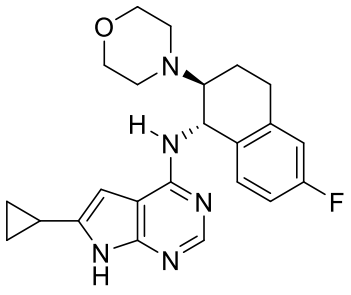
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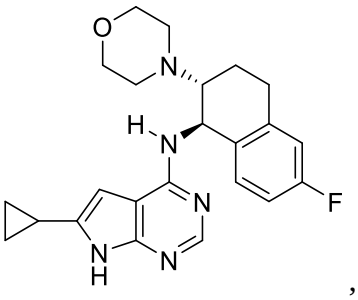
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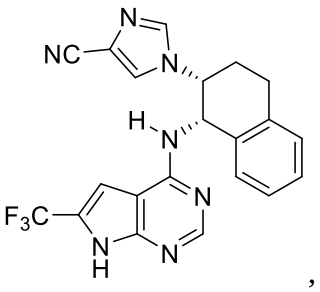
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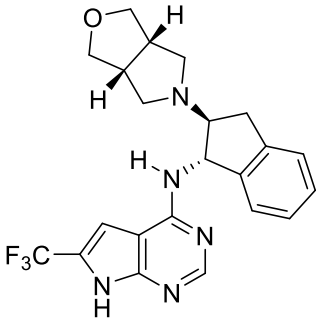
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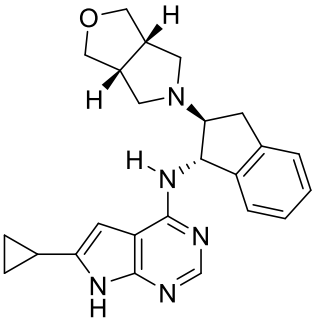
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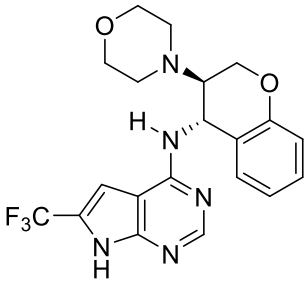
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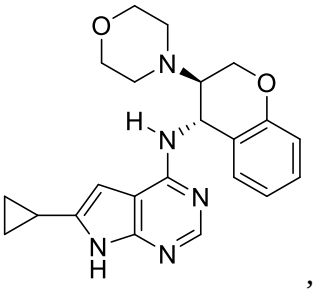
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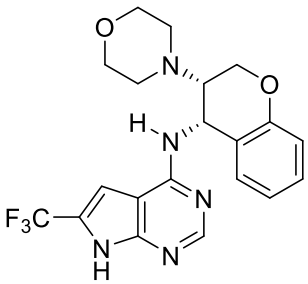
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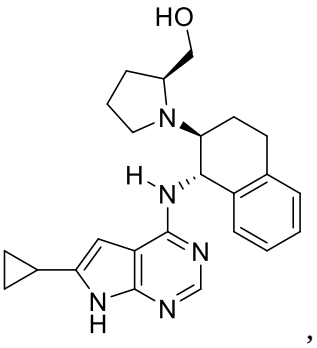
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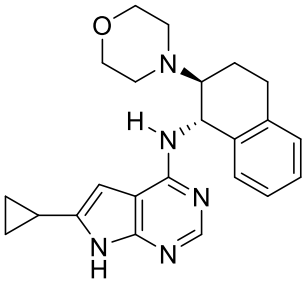
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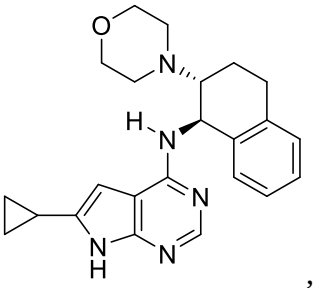
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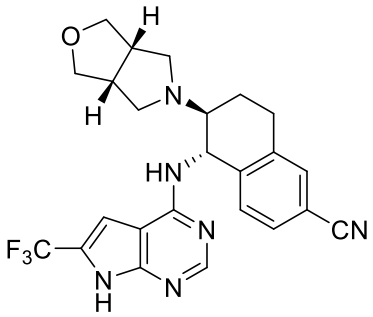
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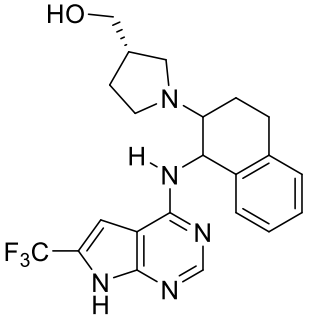
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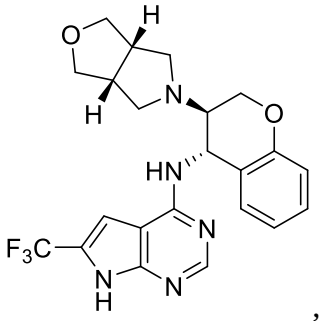
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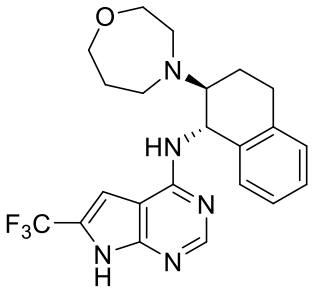
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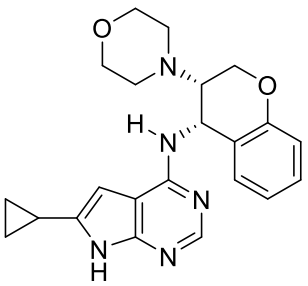
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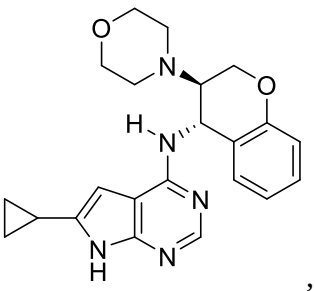
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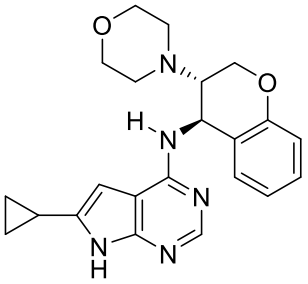
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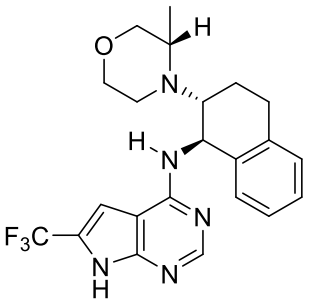
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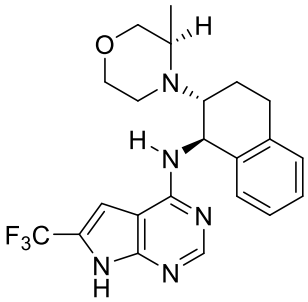
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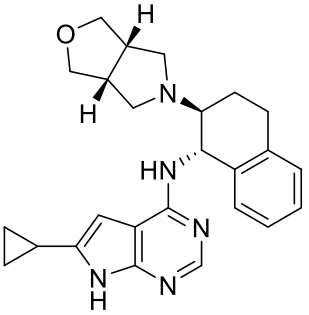
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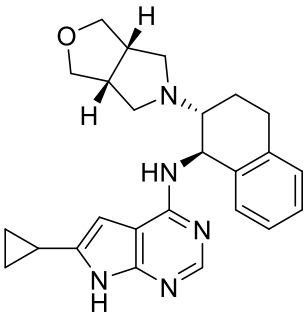
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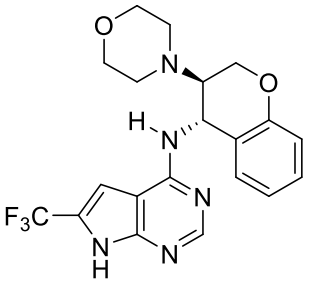
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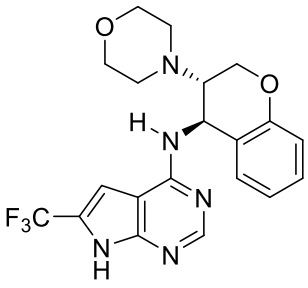
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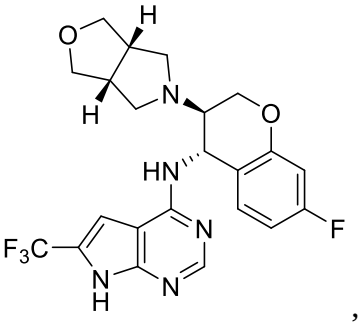
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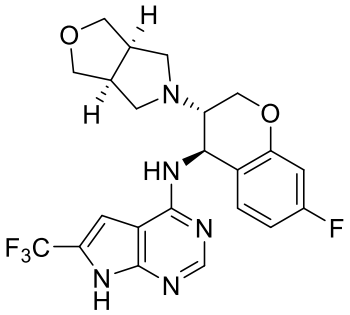
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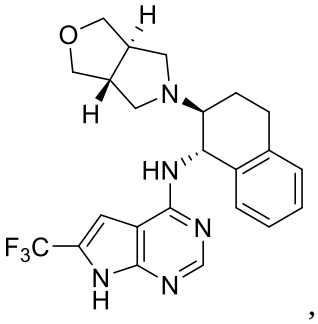
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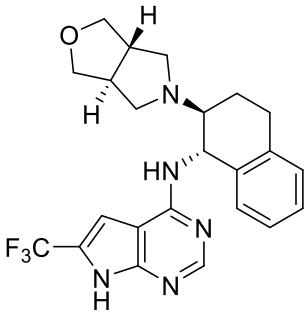
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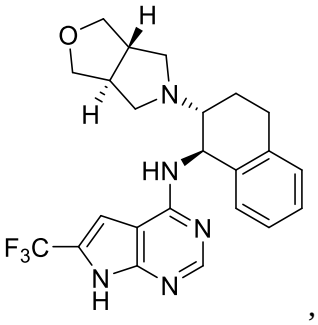
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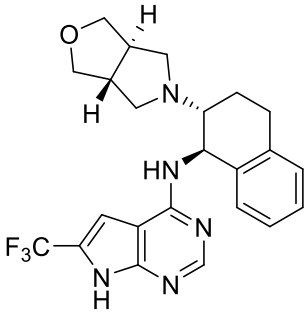
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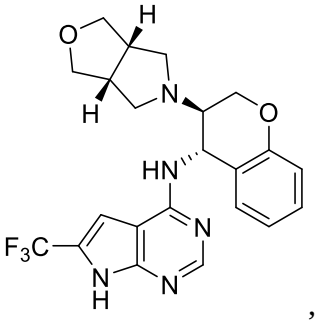
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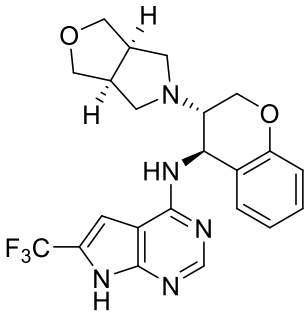
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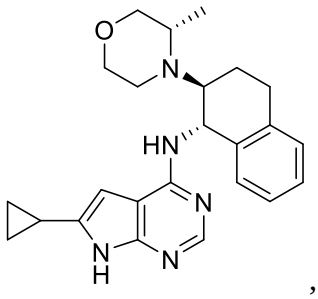
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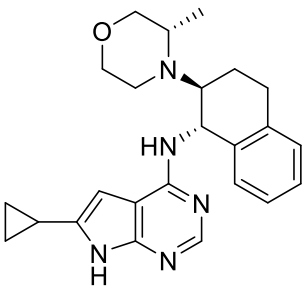
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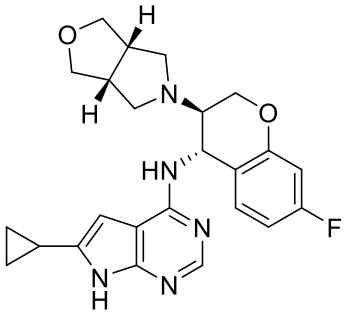
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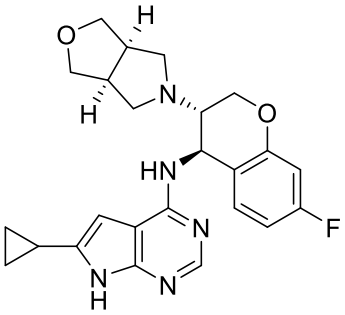
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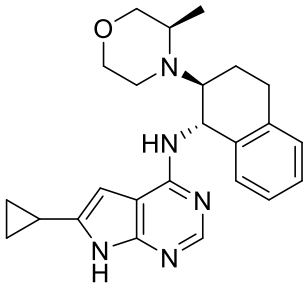
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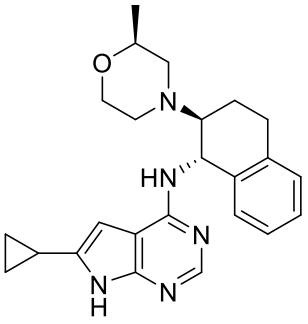
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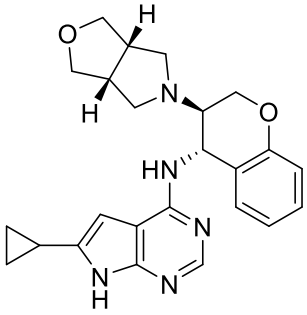
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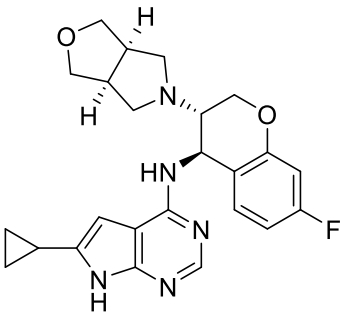
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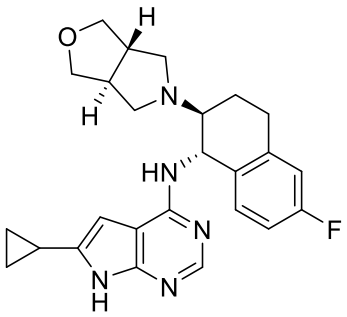
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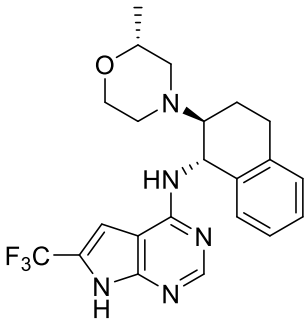
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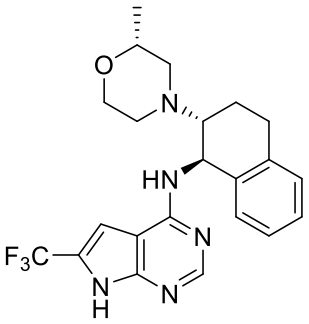
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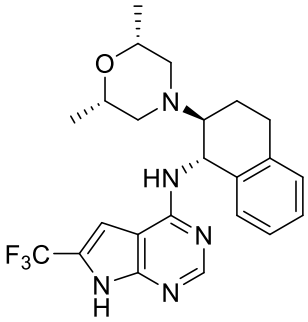
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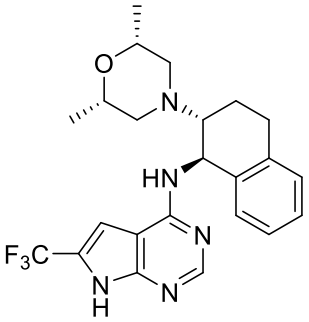
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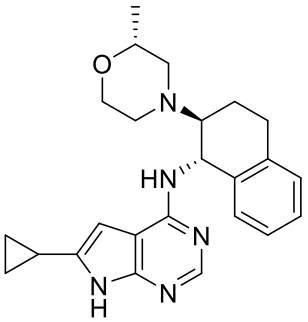
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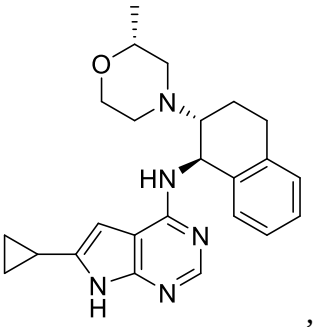
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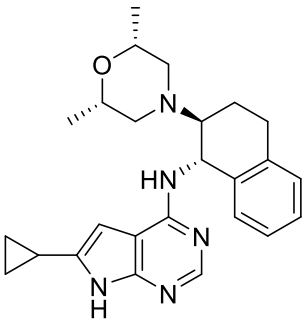
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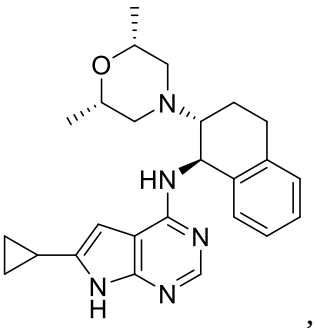
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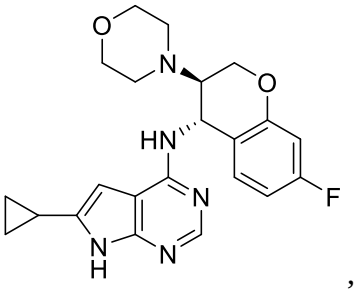
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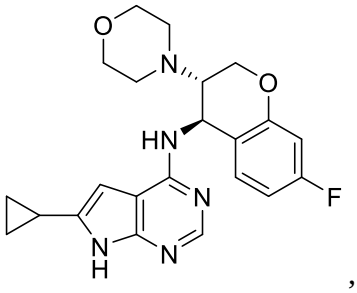
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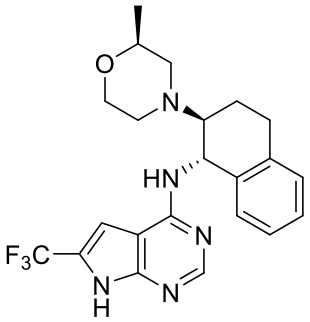
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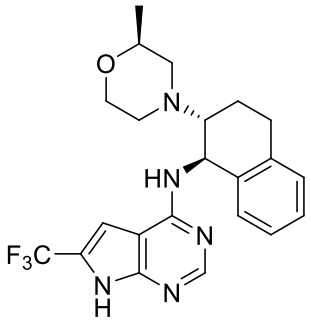
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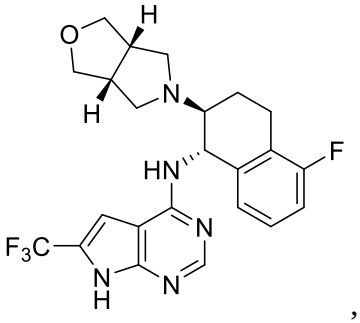
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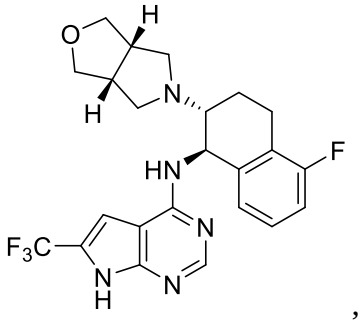
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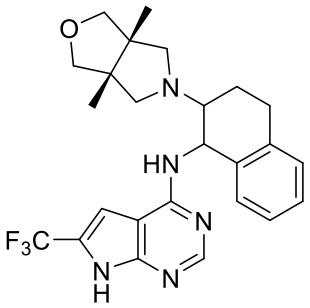
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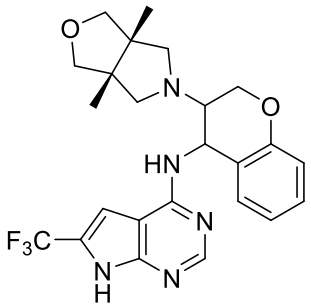
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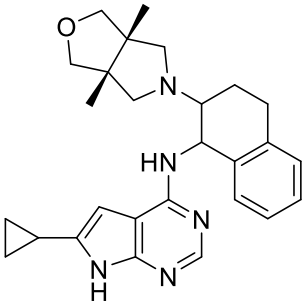
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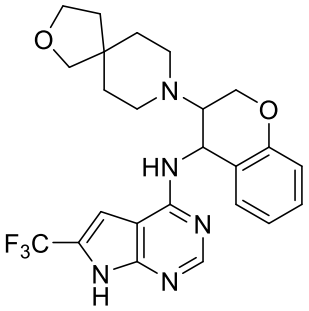
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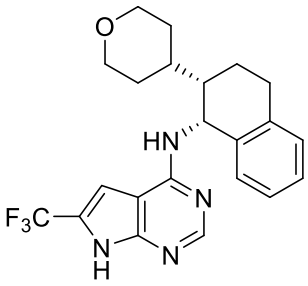
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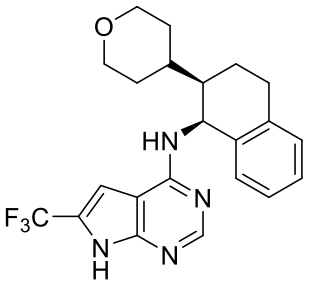
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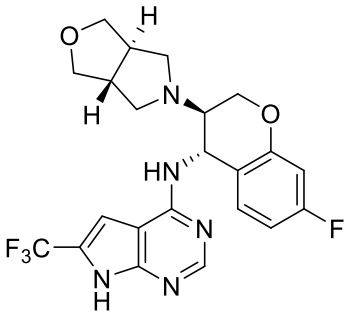
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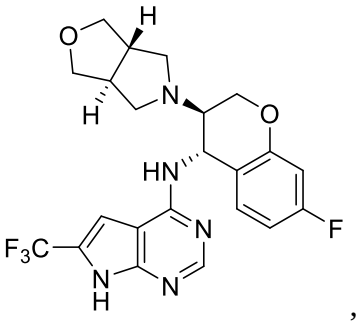
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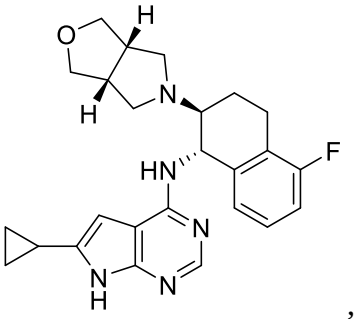
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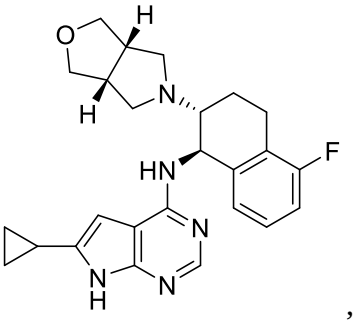
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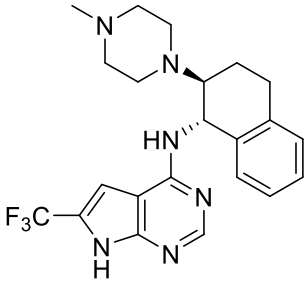
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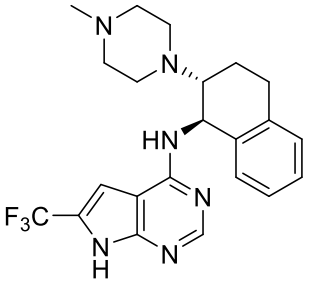
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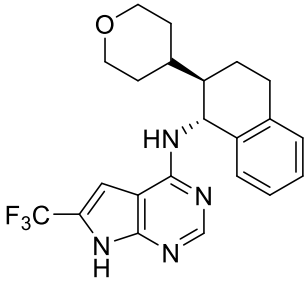
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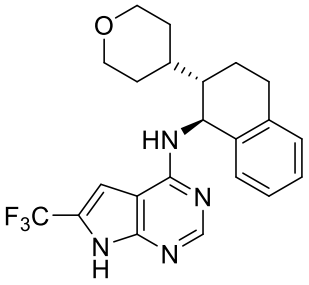
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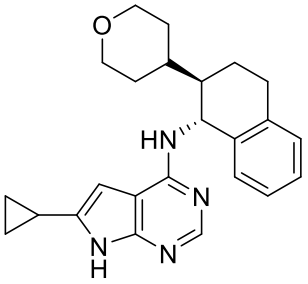
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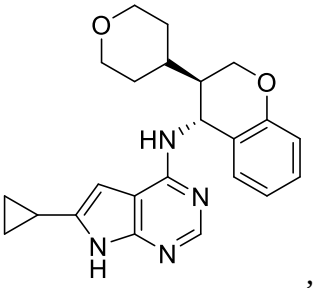
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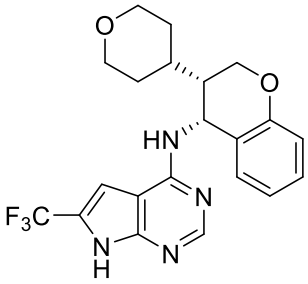
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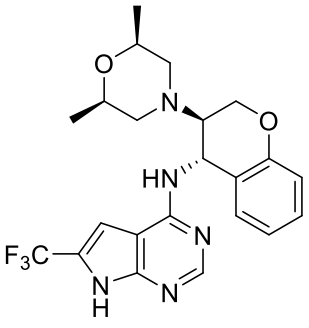
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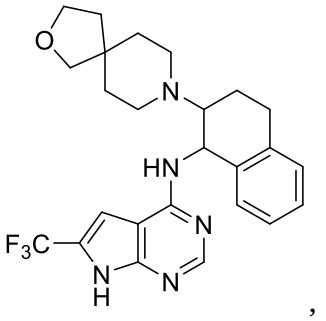
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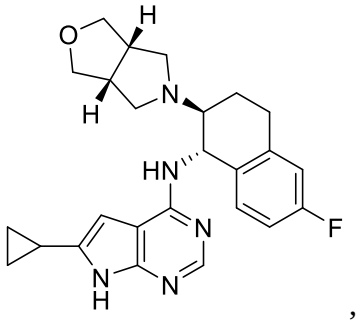
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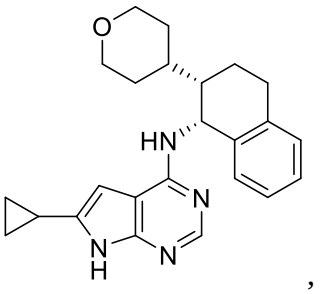
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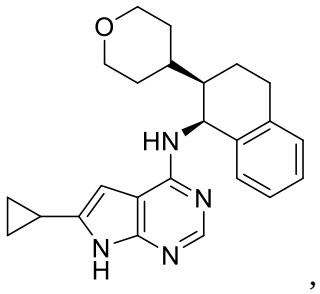
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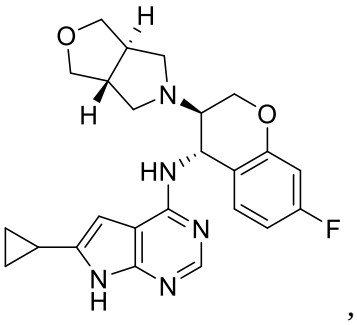
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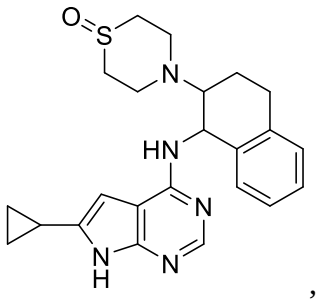
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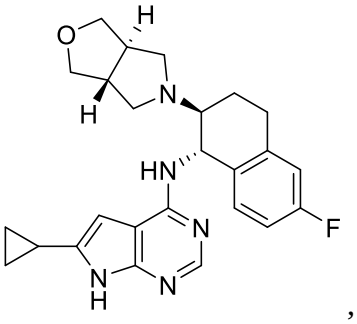
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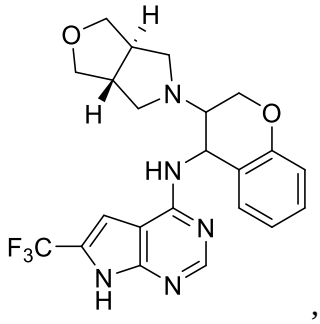
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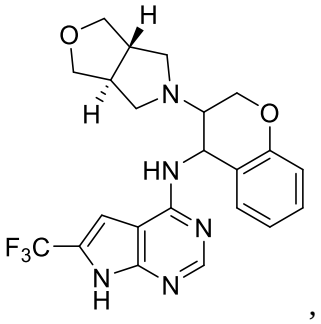
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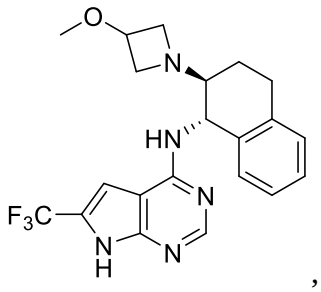
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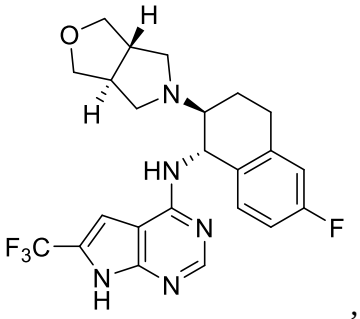
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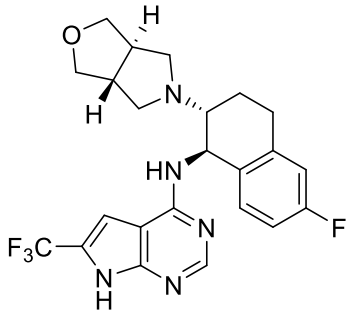
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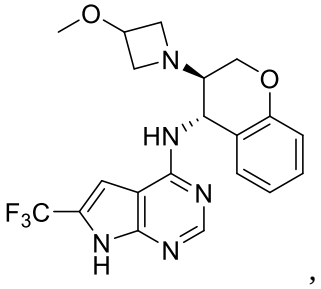
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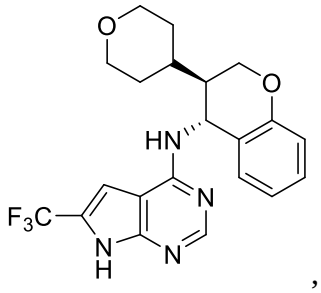
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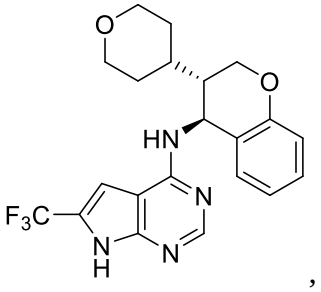
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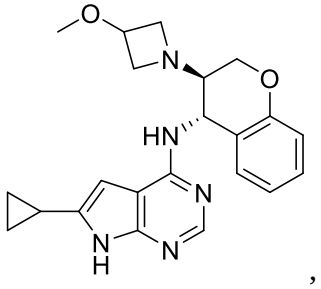
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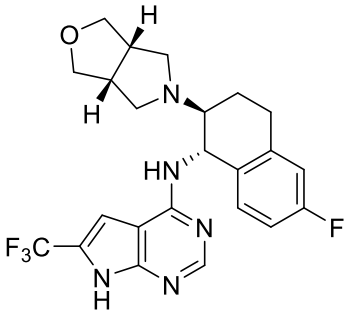
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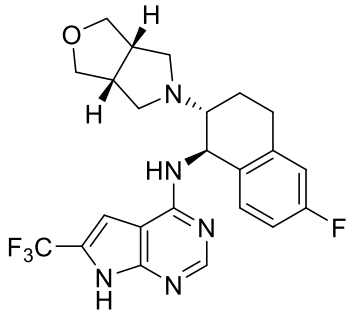
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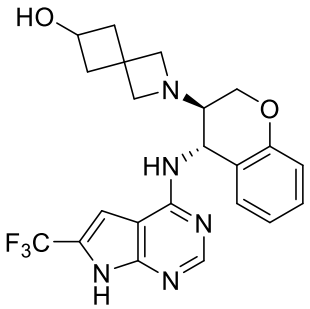
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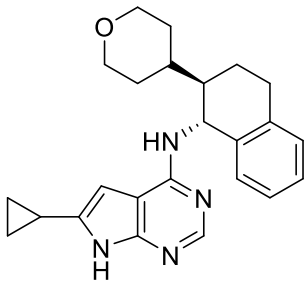
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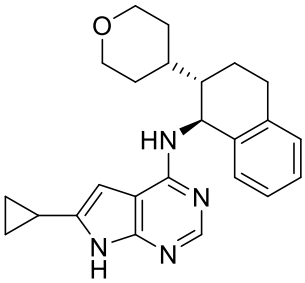
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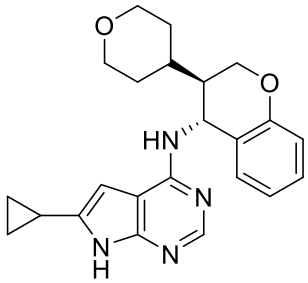
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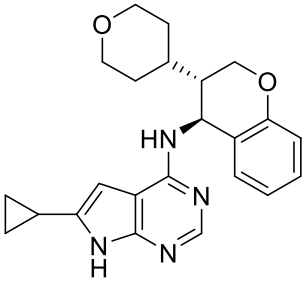
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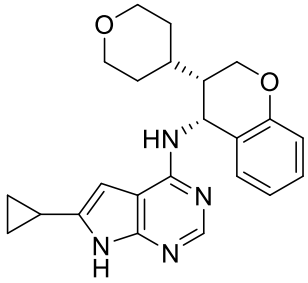
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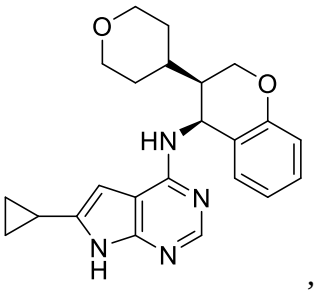
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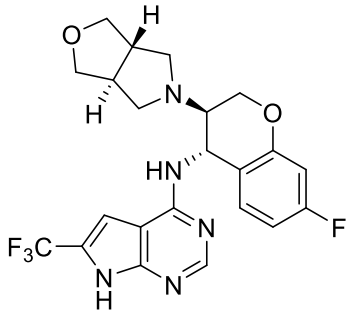
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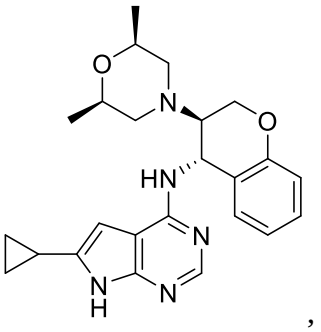
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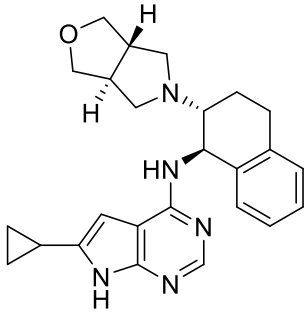
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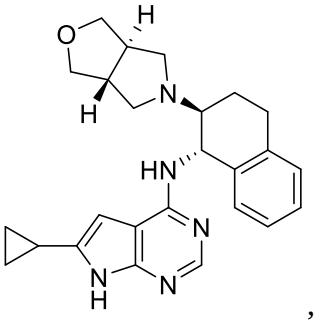
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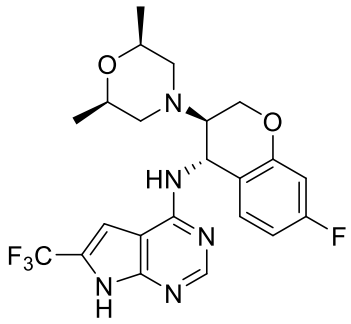
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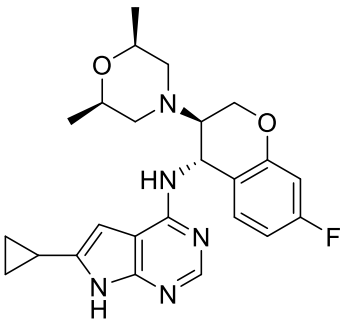
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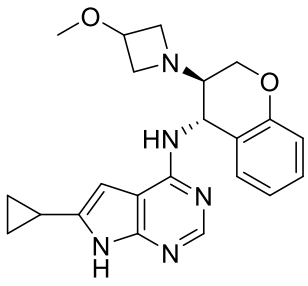
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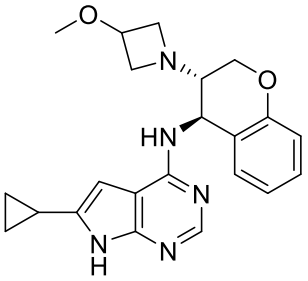
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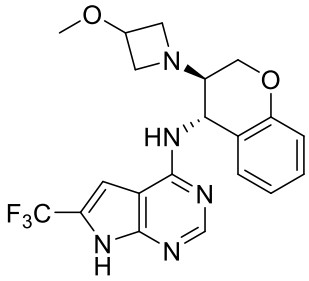
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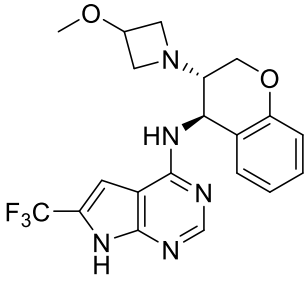
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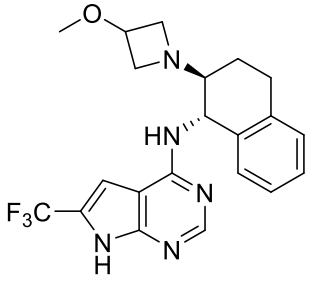
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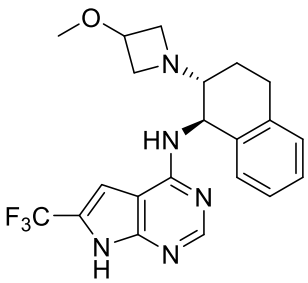
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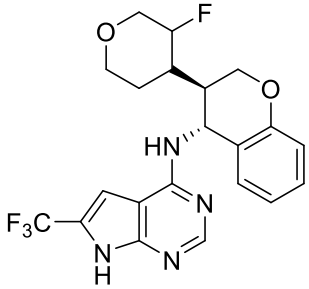
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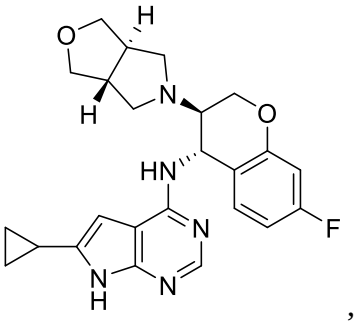
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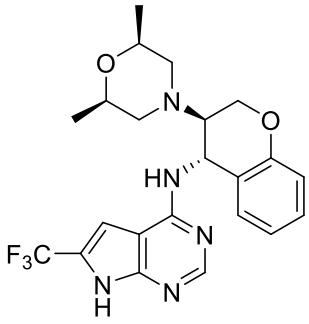
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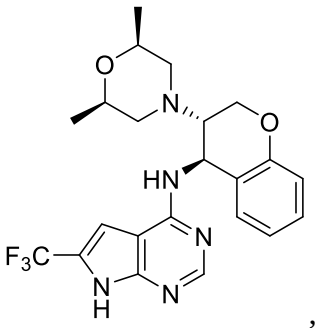
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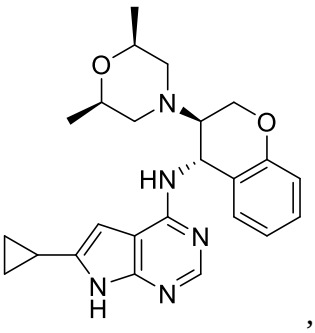
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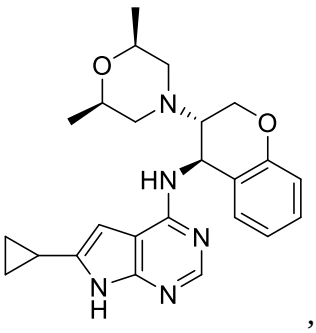
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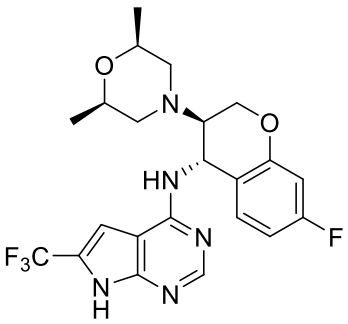
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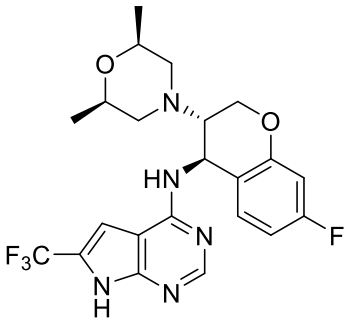
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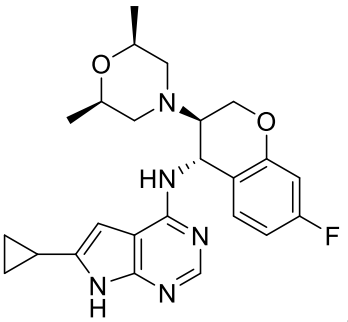
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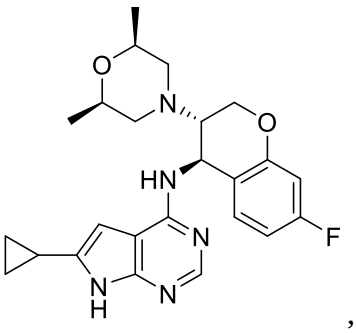
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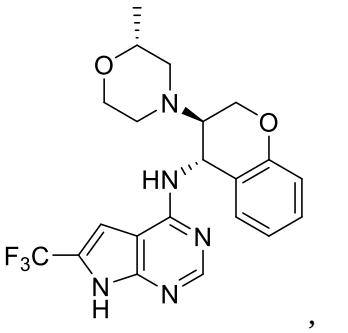
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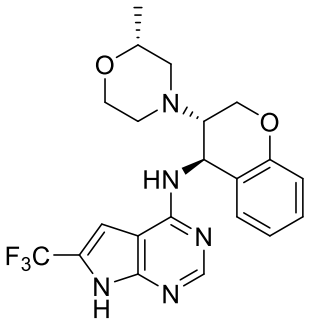
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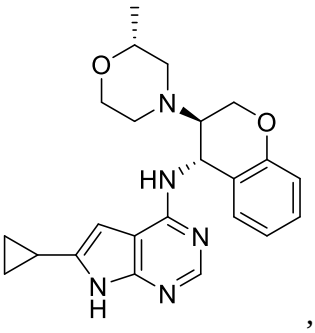
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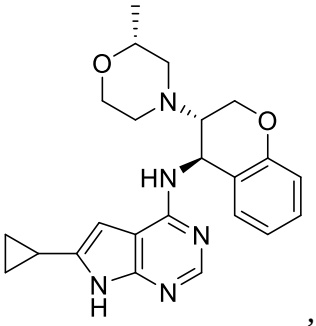
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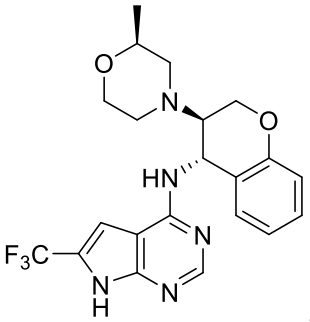
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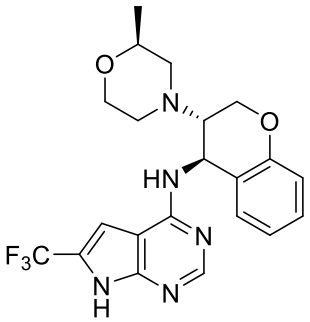
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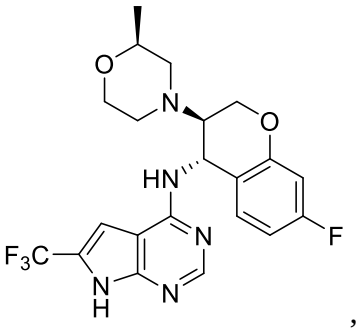
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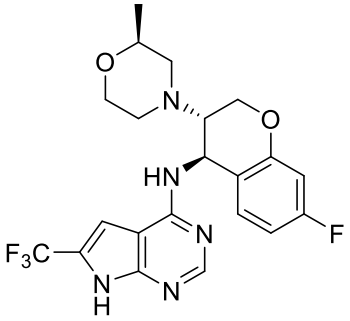
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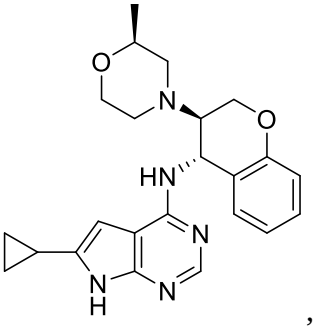
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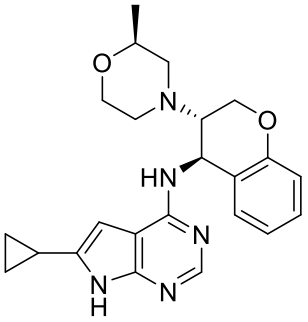
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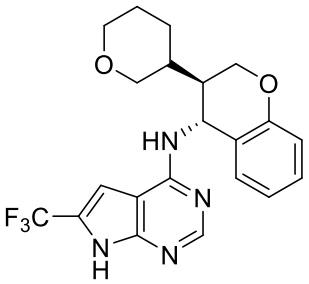
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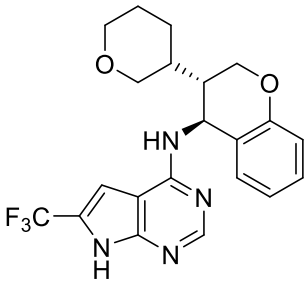
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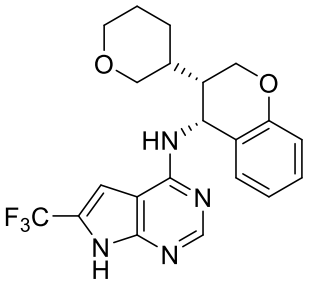
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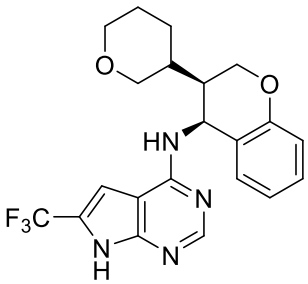
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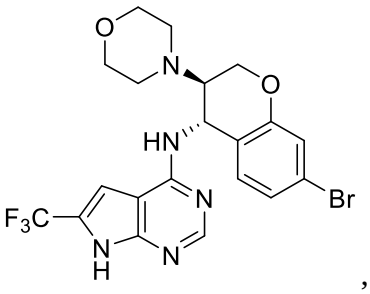
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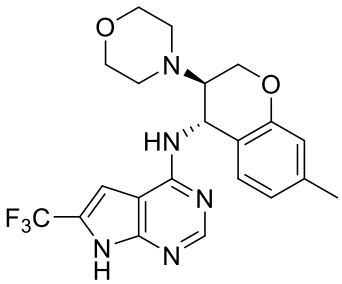
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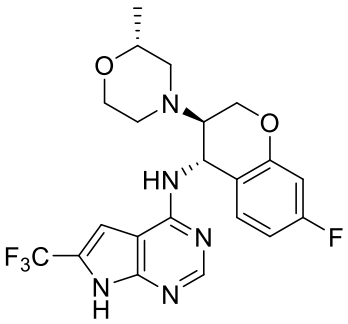
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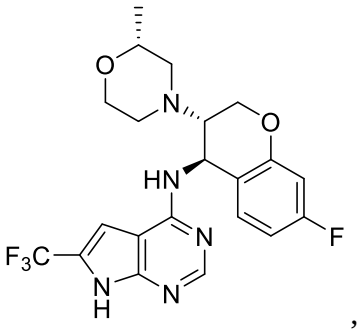
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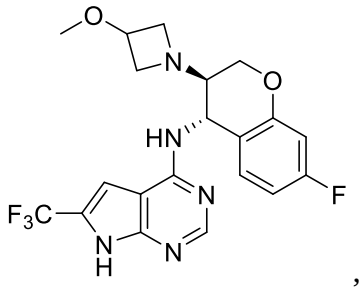
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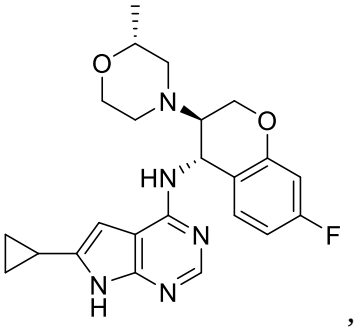
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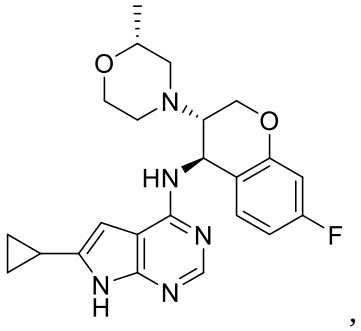
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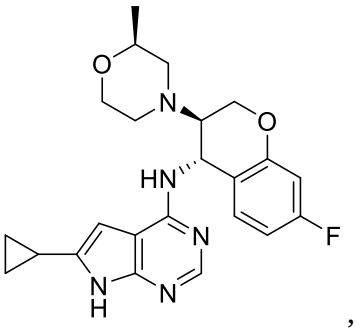
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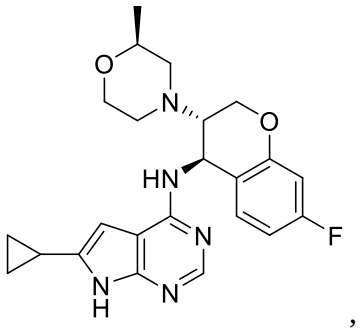
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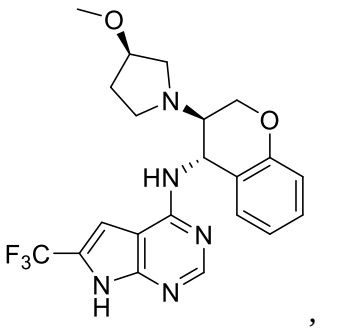
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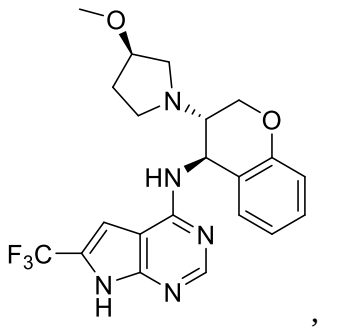
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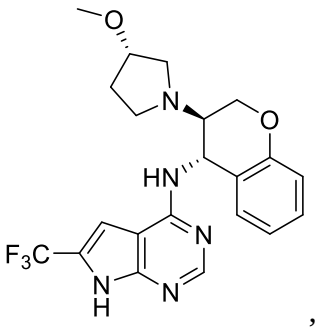
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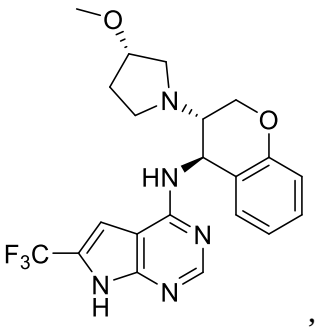
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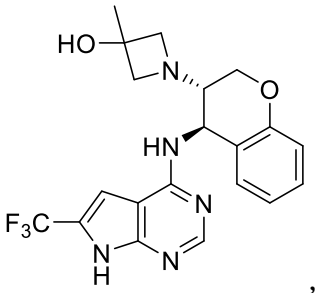
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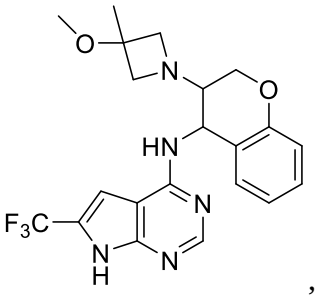
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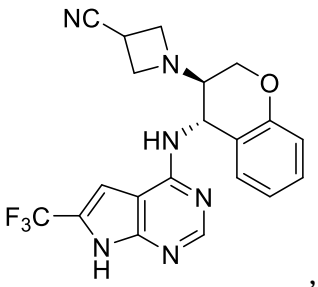
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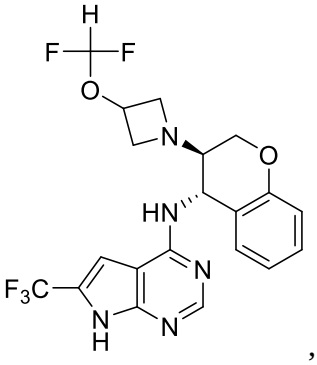
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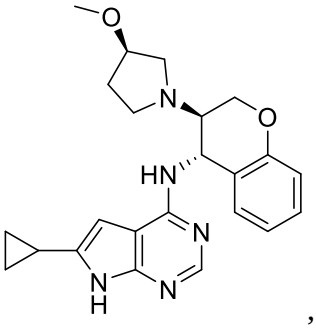
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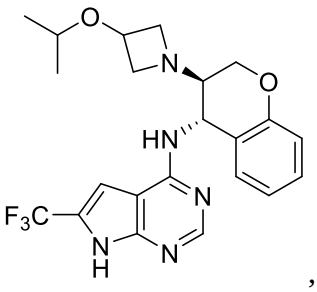
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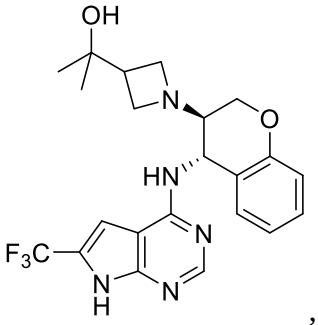
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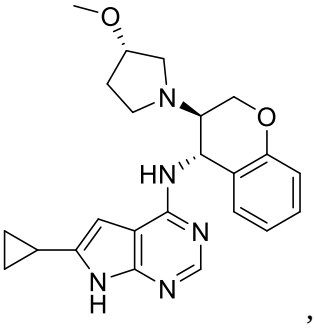
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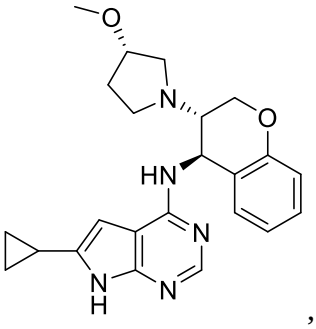
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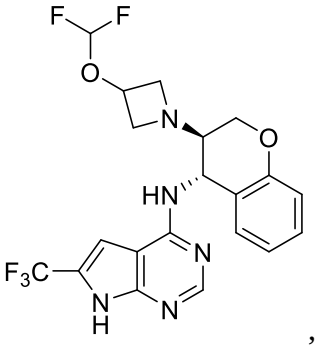
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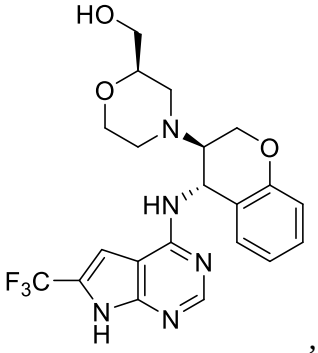
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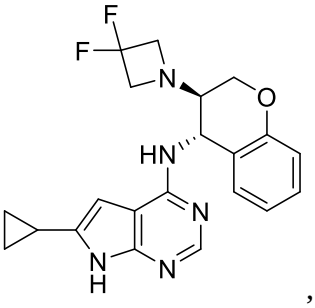
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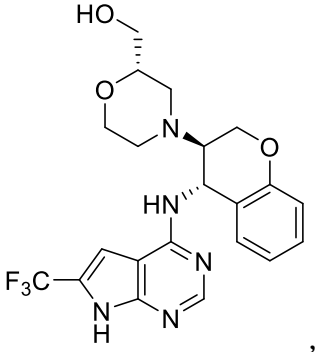
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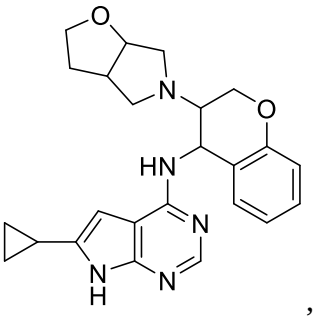
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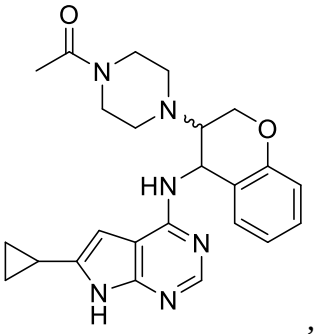
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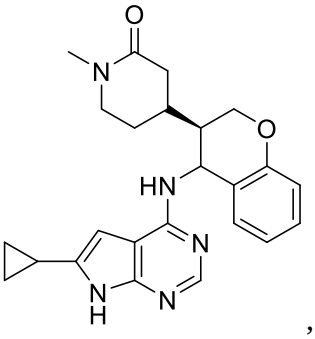
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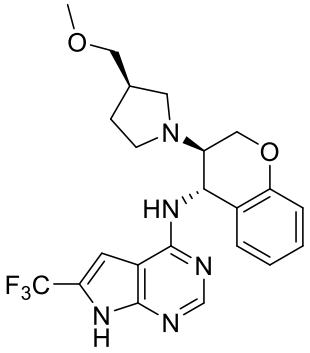
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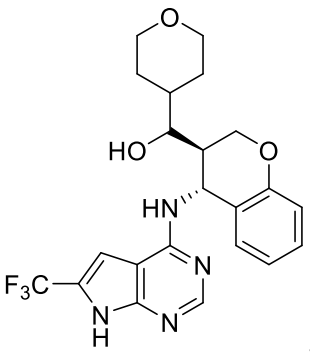
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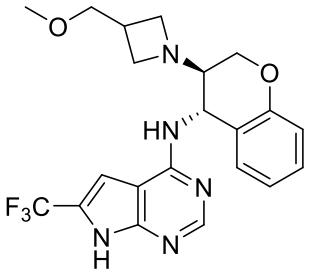
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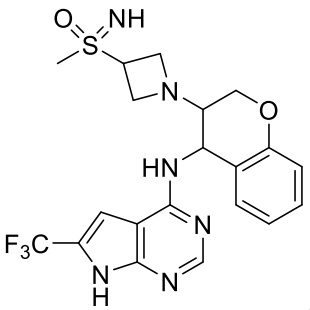
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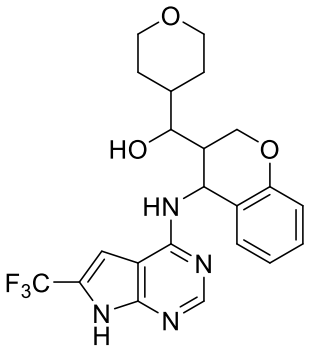
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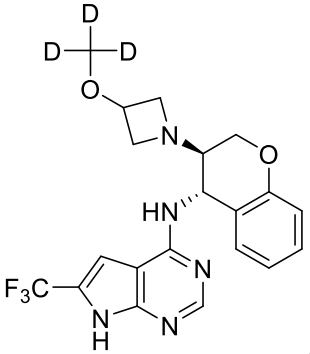
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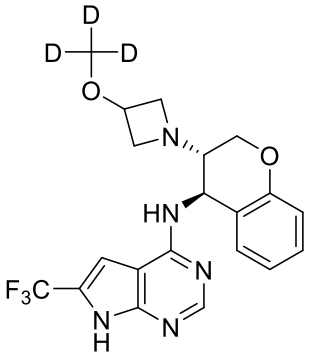
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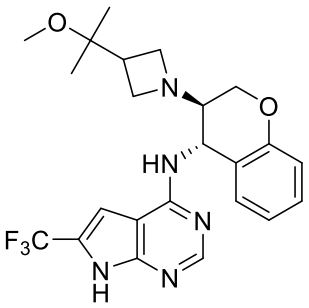
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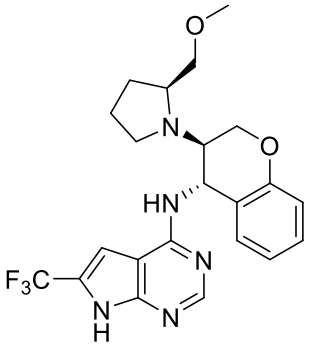
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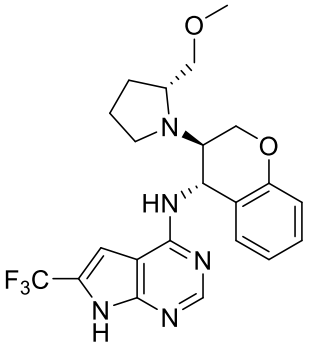
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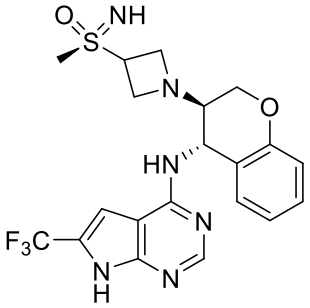
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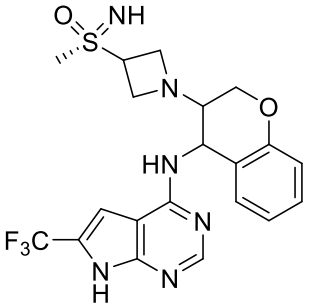
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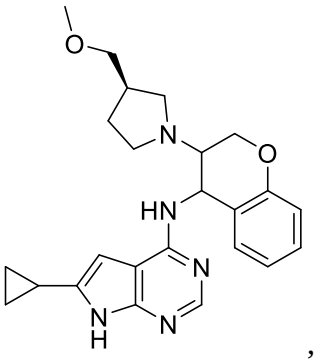
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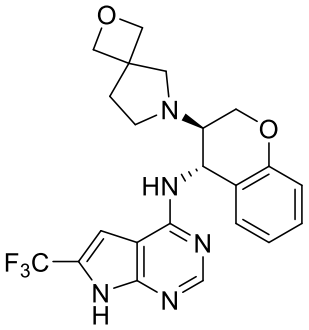
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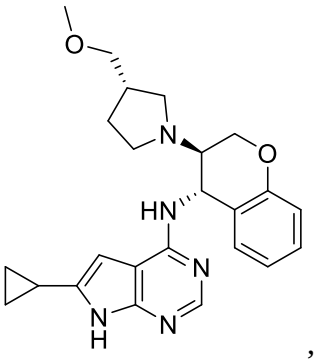
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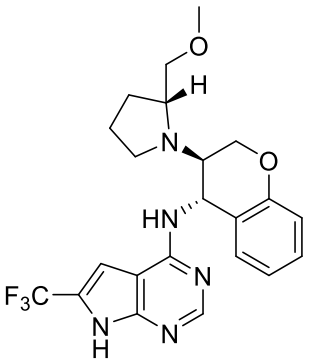
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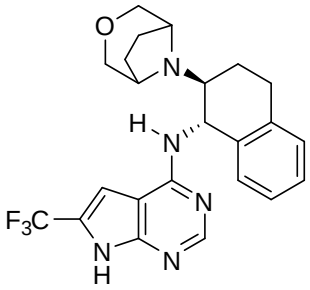
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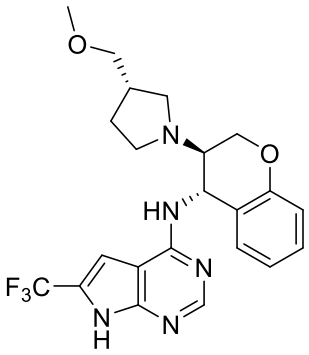
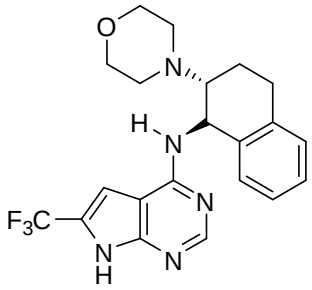

and .

32. The compound of claim 1, wherein the compound is: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33. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of claims 1-32, and a pharmaceutically acceptable carrier.

34. Use of ~~A method of modulating PINK1 kinase activity in a subject in need thereof, the method comprising administering to the subject in need thereof~~ an effective amount of the compound of any one of claims 1-32 in the manufacture of a medicament for modulating PINK1 kinase activity in a subject in need thereof.

35. The ~~method~~ use of claim 34, wherein the modulating is inhibiting.

36. A method of modulating PINK1 kinase activity in at least one cell, the method comprising contacting the cell with an effective amount of the compound of any one of claims 1-32.

37. The method of claim 36, wherein the cell is mammalian.

38. The method of claim 37, wherein the cell has been isolated from a mammal prior to the contacting step.

39. The method of claim 36, wherein the cell comprises a dysfunctional PINK1 kinase activity.

40. The method of claim 36, wherein the step of contacting is performed *in vitro*.

41. Use of ~~A method of treating a disorder in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount of~~ the compound of any one of claims 1-32 in the manufacture of a medicament for the treatment of a disorder in a subject in need thereof, wherein the disorder is a neurodegenerative disorder, a mitochondrial disorder, a fibrosis, or cardiomyopathy.

42. The ~~method~~ use of claim 41, wherein the subject is a mammal.

43. The ~~method~~use of claim 41, wherein the subject is a human.

44. The use~~method~~ of claim 41, wherein the subject has been diagnosed with the disorder prior to ~~the~~ administration of the medicament to be administered~~ering step~~.

45. The use~~method~~ of claim 41, wherein the medicament is to be administer~~inged is accomplished~~ by oral adminstration, parenteral administration, sublingual administration, transdermal administration, rectal administration, transmucosal administration, topical administration, inhalation, buccal administration, intrapleural administration, intravenous administration, intraarterial administration, intraperitoneal administration, subcutaneous administration, intramuscular administration, intranasal administration, intrathecal administration, and intraarticular administration, or combinations thereof.

46. The ~~method~~ use of claim 41, ~~wherein the administering~~further compris~~es~~ing ~~adminsitering~~ from about 1 to about 2000 micrograms of expressible nucleic acid sequence to be administered.

47. The ~~method~~ use of claim 41, wherein the neurodegenerative disorder is Parkinson's disease, Huntington's disease, or amyotrophic lateral sclerosis.

48. A compound of any one of claims 1-32 for use as a medicament.

~~48.~~49. A kit comprising the compound of any one of claims 1-32, and one or more of:

(a) at least one agent known for the treatment of a neurodegenerative disorder, a mitochondrial disorder, a fibrosis, and cardiomyopathy;

(b) instructions for administering the compound in connection with the neurodegenerative disorder, a mitochondrial disorder, a fibrosis, or cardiomyopathy; and/or

(c) instructions for treating the disorder.