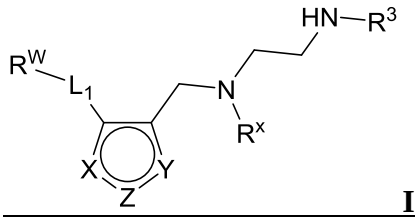
Claims

What is claimed is:

1. A compound of Formula (**I**):



I

or a pharmaceutically acceptable salt thereof,

wherein

X is N, Z is NR^4, and Y is CR^5; or

X is NR^4, Z is N, and Y is CR^5; or

X is CR^5, Z is NR^4, and Y is N; or

X is CR^5, Z is N, and Y is NR^4;

R^x is optionally substituted C_{1-4} alkyl or optionally substituted C_{3-4} cycloalkyl;

L_1 is a bond, -O-, $-N(R^B)$-, -S-, -C(O)-, -C(O)O-, -C(O)S-, $-C(O)N(R^B)$-, $-C(O)N(R^B)N(R^B)$-, -OC(O)-, $-OC(O)N(R^B)$-, $-NR^BC(O)$-, $-NR^BC(O)N(R^B)$-, $-NR^BC(O)N(R^B)N(R^B)$-, $-NR^BC(O)O$-, -SC(O)-, $-C(=NR^B)$-, $-C(=NNR^B)$-, $-C(=NOR^A)$-, $-C(=NR^B)N(R^B)$-, $-NR^BC(=NR^B)$-, -C(S)-, $-C(S)N(R^B)$-, $-NR^BC(S)$-, -S(O)-, $-OS(O)_2$-, $-S(O)_2O$-, $-SO_2$-, $-N(R^B)SO_2$-, $-SO_2N(R^B)$-, or an optionally substituted C_{1-6} saturated or unsaturated hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain is optionally and independently replaced with -O-, $-N(R^B)$-, -S-, -C(O)-, -C(O)O-, -C(O)S-, $-C(O)N(R^B)$-, $-C(O)N(R^B)N(R^B)$-, -OC(O)-, $-OC(O)N(R^B)$-, $-NR^BC(O)$-, $-NR^BC(O)N(R^B)$-, $-NR^BC(O)N(R^B)N(R^B)$-, $-NR^BC(O)O$-, -SC(O)-, $-C(=NR^B)$-, $-C(=NNR^B)$-, $-C(=NOR^A)$-, $-C(=NR^B)N(R^B)$-, $-NR^BC(=NR^B)$-, -C(S)-, $-C(S)N(R^B)$-, $-NR^BC(S)$-, -S(O)-, $-OS(O)_2$-, $-S(O)_2O$-, $-SO_2$-, $-N(R^B)SO_2$-, or $-SO_2N(R^B)$-;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally

substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group, or an R^B and R^W on the same nitrogen atom may be taken together with the intervening nitrogen to form an optionally substituted heterocyclic ring;

R^W is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; provided that when L_1 is a bond, R^W is not optionally substituted aryl or optionally substituted heteroaryl;

R^3 is hydrogen, C_{1-4} alkyl, or C_{3-4} cycloalkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl; or optionally substituted C_{1-4} alkyl-Cy;

Cy is optionally substituted C_{3-7} cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

R^5 is hydrogen, halo, -CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{3-4} cycloalkyl;

wherein, and unless otherwise specified,

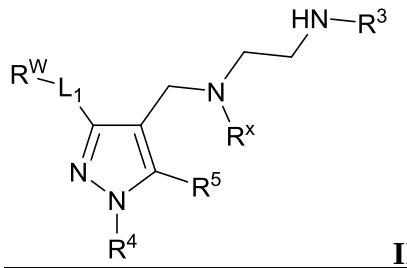
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

carbocyclyl or carbocyclic refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms and zero heteroatoms in the non–aromatic ring system;

aryl refers to a radical of a monocyclic or polycyclic aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

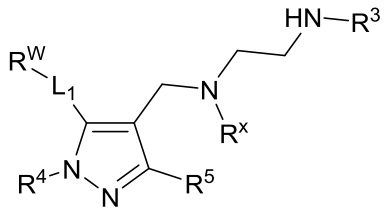
2. The compound of claim 1, wherein the compound is of Formula (**II**):



II

or a pharmaceutically acceptable salt thereof.

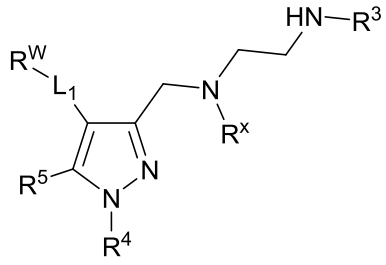
3. The compound of claim 1, wherein the compound is of Formula (**III**):



III

or a pharmaceutically acceptable salt thereof.

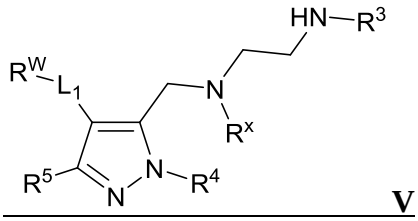
4. The compound of claim 1, wherein the compound is of Formula (**IV**):



IV

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein the compound is of Formula (**V**):



V

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1-5, wherein L_1 is a bond and R^w is optionally substituted carbocyclyl.

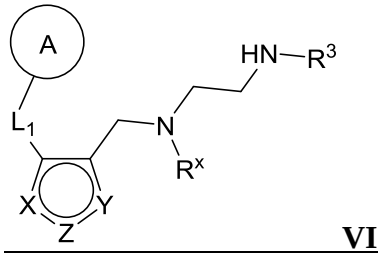
7. The compound of claim 6, wherein R^w is optionally substituted cyclohexyl.

8. The compound of any one of claims 1-5, wherein L_1 is a bond and R^w is optionally substituted heterocyclyl.

9. The compound of claim 8, wherein R^w is optionally substituted piperidine.

10. The compound of any one of claims 1-5, wherein L_1 is C_{1-4} alkylene and R^W is optionally substituted aryl or optionally substituted heteroaryl.

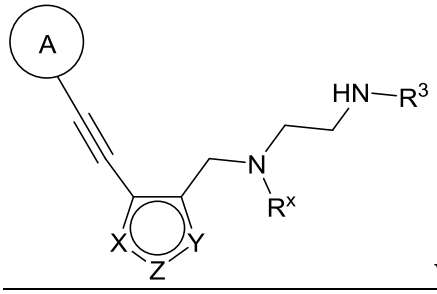
11. The compound of claim 1, wherein the compound is of Formula (**VI**):



VI

or a pharmaceutically acceptable salt thereof, wherein Ring A is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

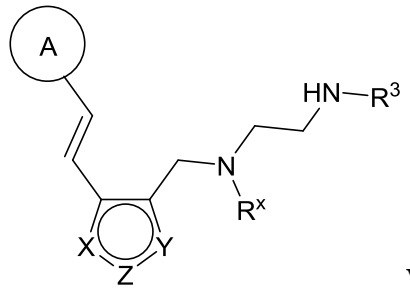
12. The compound of claim 11, wherein the compound is of Formula (**VI-a**):



VI-a

or a pharmaceutically acceptable salt thereof.

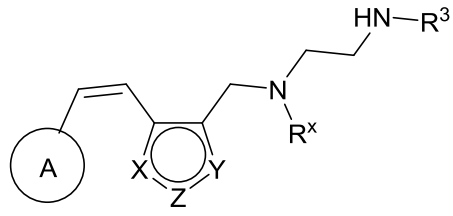
13. The compound of claim 11, wherein the compound is of Formula (**VI-b**):



VI-b

or a pharmaceutically acceptable salt thereof.

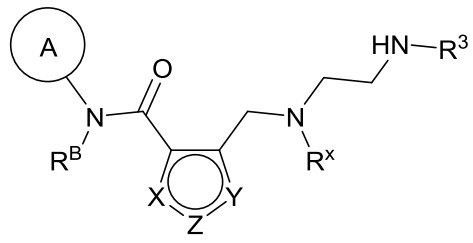
14. The compound of claim 11, wherein the compound is of Formula (**VI-c**):



VI-c

or a pharmaceutically acceptable salt thereof.

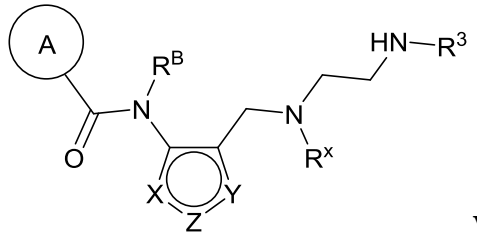
15. The compound of claim 11, wherein the compound is of Formula (**VI-d**):



VI-d

or a pharmaceutically acceptable salt thereof.

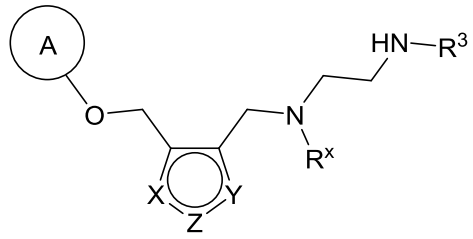
16. The compound of claim 11, wherein the compound is of Formula (**VI-e**):



VI-e

or a pharmaceutically acceptable salt thereof.

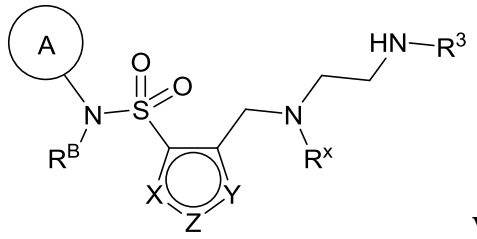
17. The compound of claim 11, wherein the compound is of Formula (**VI-f**):



VI-f

or a pharmaceutically acceptable salt thereof.

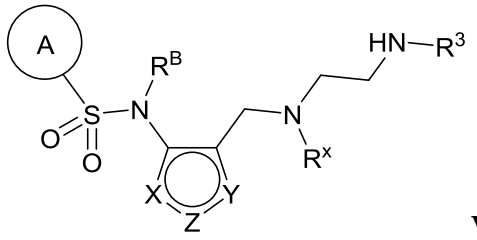
18. The compound of claim 11, wherein the compound is of Formula (**VI-g**):



VI-g

or a pharmaceutically acceptable salt thereof.

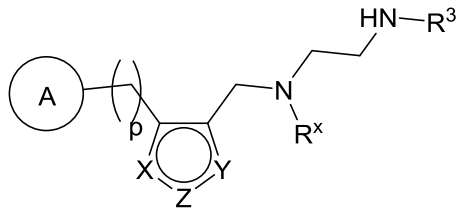
19. The compound of claim 11, wherein the compound is of Formula (**VI-h**):



VI-h

or a pharmaceutically acceptable salt thereof.

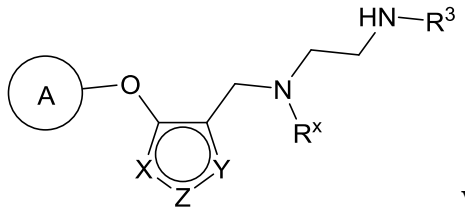
20. The compound of claim 11, wherein the compound is of Formula (**VI-i**):



VI-i

or a pharmaceutically acceptable salt thereof, wherein p is 1, 2, 3, 4, 5, or 6.

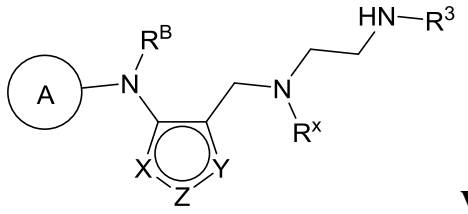
21. The compound of claim 11, wherein the compound is of Formula (**VI-j**):



VI-j

or a pharmaceutically acceptable salt thereof.

22. The compound of claim 11, wherein the compound is of Formula (**VI-k**):



VI-k

or a pharmaceutically acceptable salt thereof.

23. The compound of any one of claims 11-22, wherein Ring A is optionally substituted heteroaryl.

24. The compound of any one of claims 11-22, wherein Ring A is optionally substituted carbocyclyl.

25. The compound of any one of claims 11-22, wherein Ring A is optionally substituted heterocyclyl.

26. The compound of any one of claims 11-22, wherein Ring A is optionally substituted bicyclic carbocyclyl.

27. The compound of any one of claims 11-22, wherein Ring A is optionally substituted bicyclic heterocyclyl.

28. The compound of any one of claims 1-27, wherein R^3 is hydrogen.

29. The compound of any one of claims 1-27, wherein R^3 is C_{1-4} alkyl.

30. The compound of claim 29, wherein R^3 is methyl, ethyl, propyl, or butyl.

31. The compound of any one of claims 1-27, wherein R^3 is cyclopropyl or cyclobutyl.

32. The compound of any one of claims 1-31, wherein R^4 is hydrogen.

33. The compound of any one of claims 1-31, wherein R^4 is optionally substituted C_{1-6} alkyl.

34. The compound of claim 33, wherein R^4 is unsubstituted C_{1-6} alkyl.

35. The compound of claim 34, wherein R^4 is methyl.

36. The compound of any one of claims 1-35, wherein R^5 is hydrogen.

37. The compound of any one of claims 1-35, wherein R^5 is optionally substituted C_{1-4} alkyl.

38. The compound of claim 37, wherein R^5 is unsubstituted C_{1-4} alkyl.

39. The compound of claim 38, wherein R^5 is methyl.

40. The compound of any one of claims 1-39, wherein R^x is optionally substituted C_{1-4} alkyl.

41. The compound of claim 34, wherein R^x is unsubstituted C_{1-4} alkyl.

42. The compound of claim 41, wherein R^x is methyl.

43. The compound of claim 41, wherein R^x is ethyl.

44. The compound of claim 41, wherein R^x is isopropyl.

45. The compound of claim 40, wherein R^x is substituted C_{1-4} alkyl.

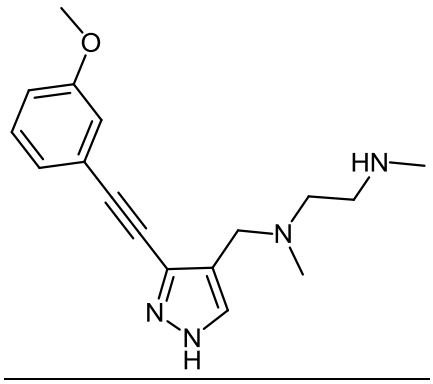
46. The compound of claim 45, wherein R^x is hydroxyethyl or methoxyethyl.

47. The compound of any one of claims 1-39, wherein R^x is optionally substituted C_{3-4} cycloalkyl.

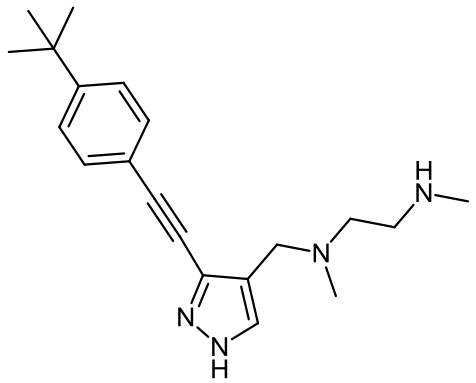
48. The compound of claim 47, wherein R^x is cyclopropyl.

49. The compound of claim 1, wherein the compound is selected from the group consisting of:

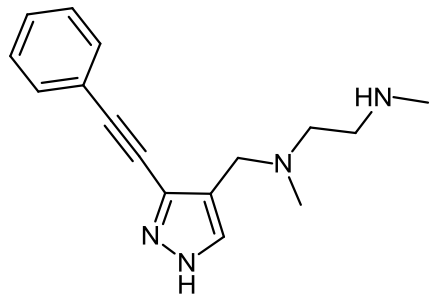
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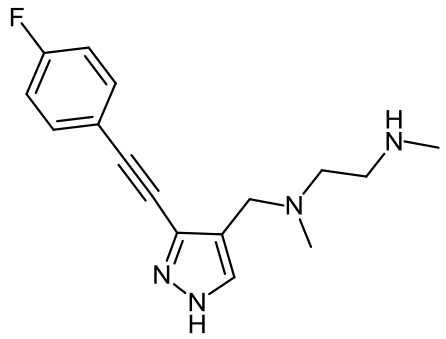
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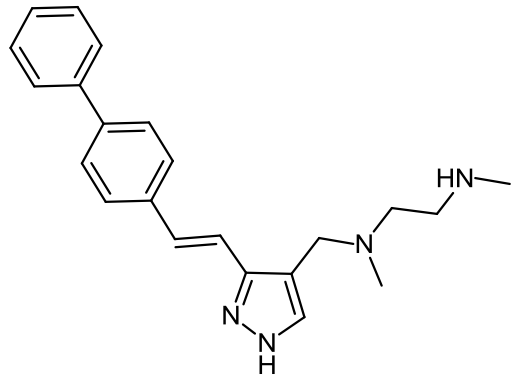
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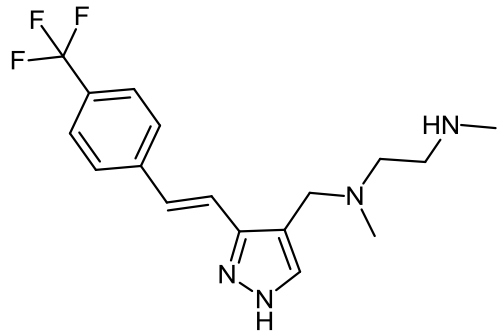
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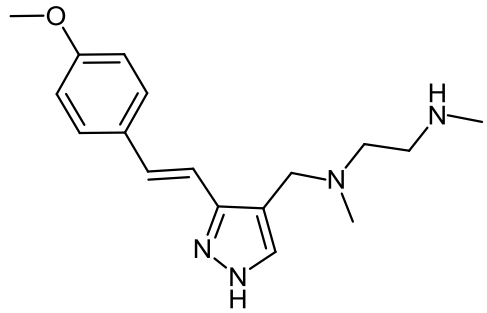
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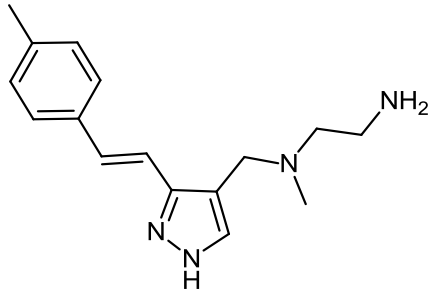
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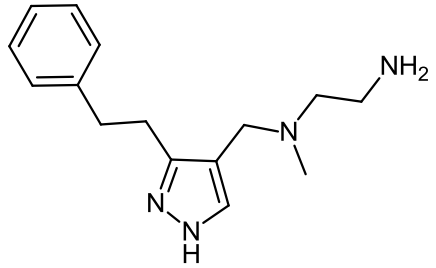
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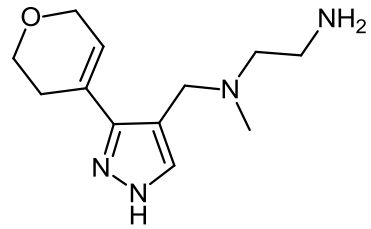
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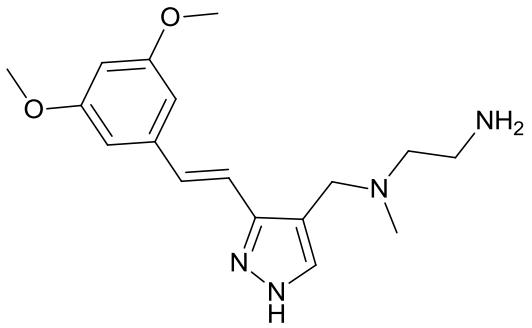
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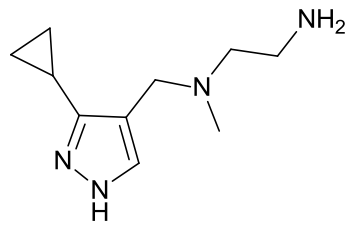
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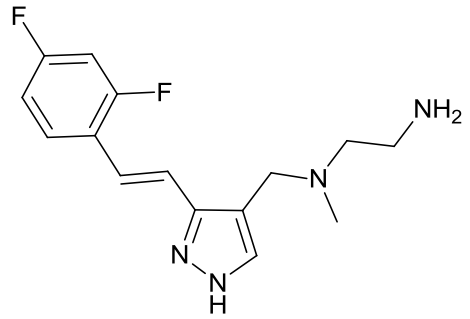
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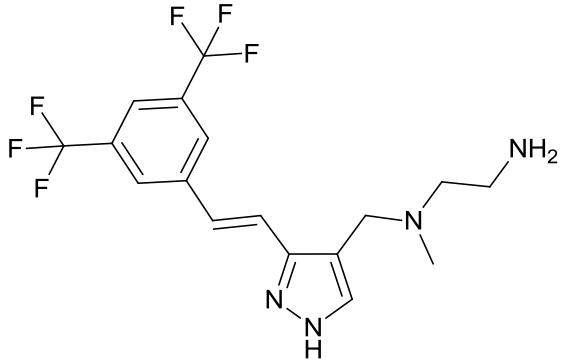
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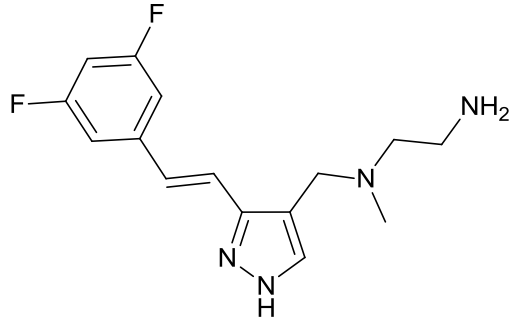
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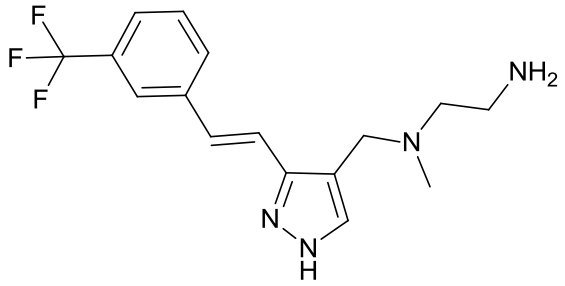
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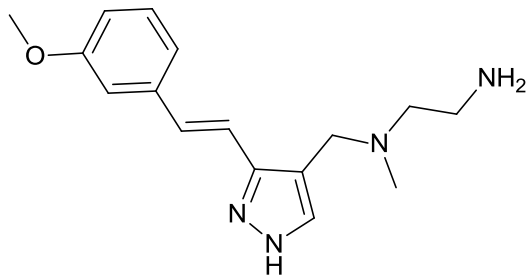
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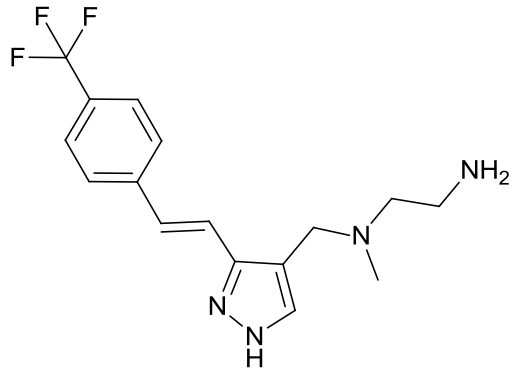
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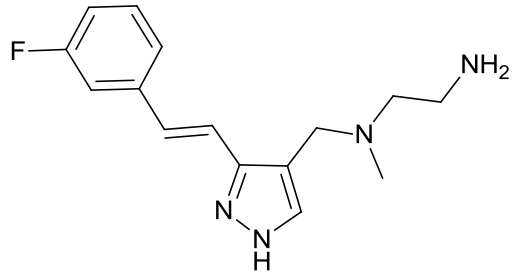
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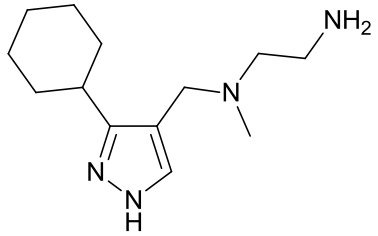
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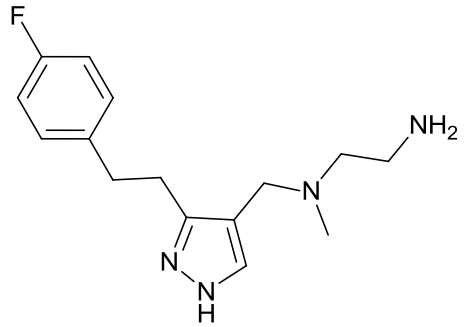
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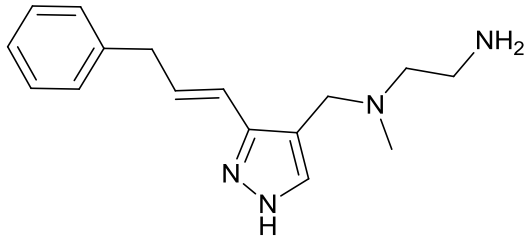
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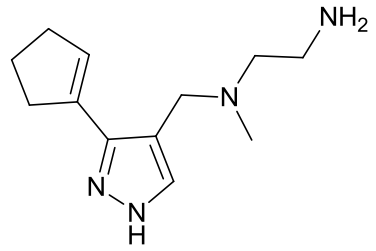
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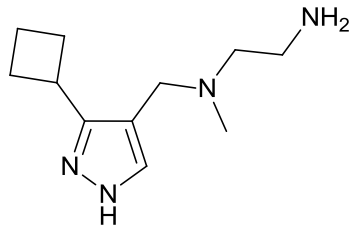
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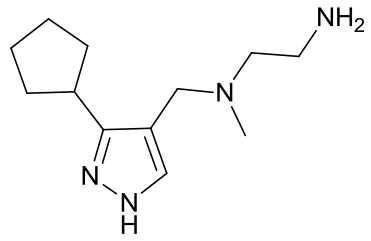
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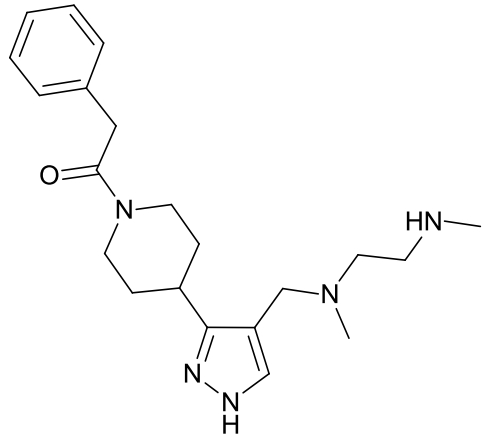
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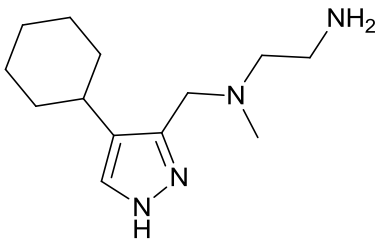
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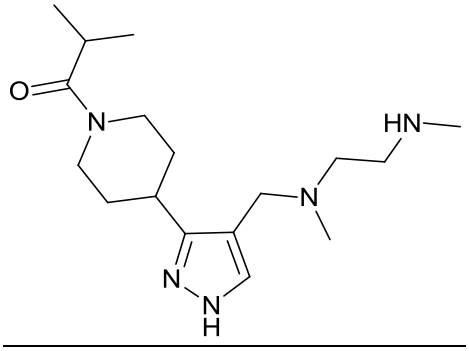
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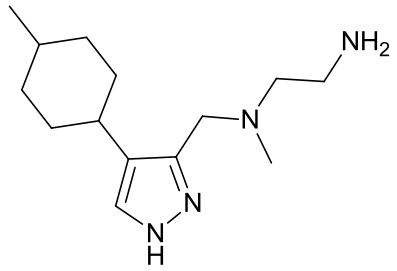
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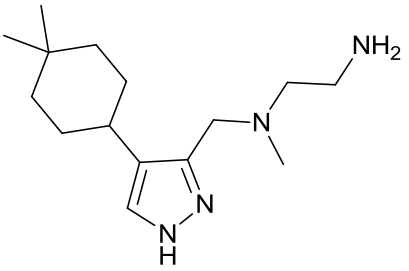
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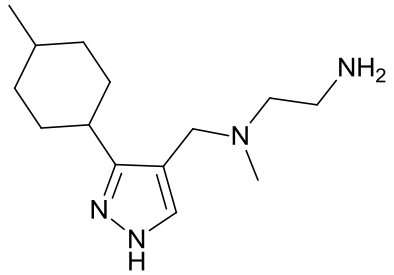
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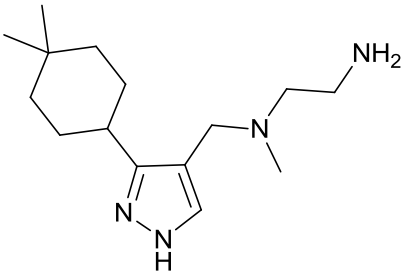
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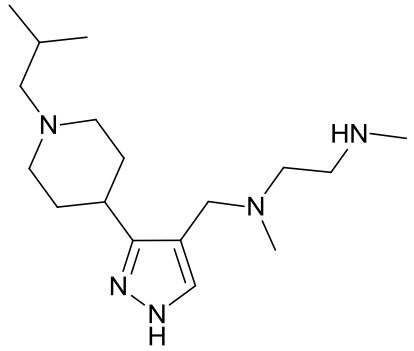
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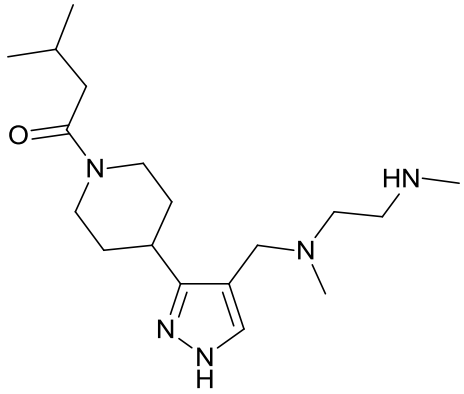
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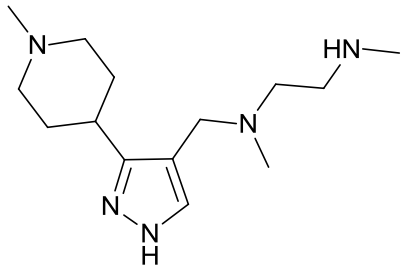
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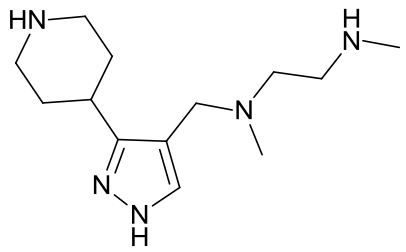
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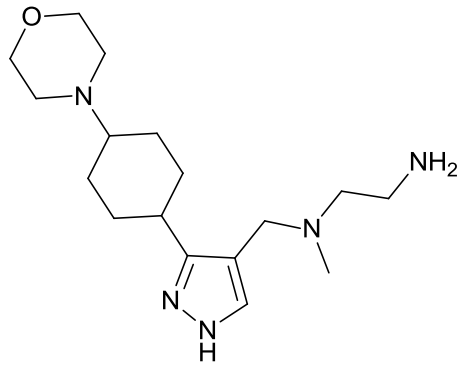


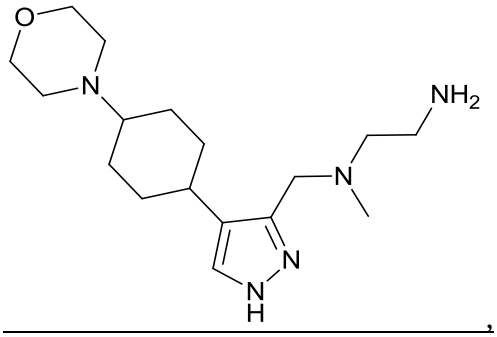
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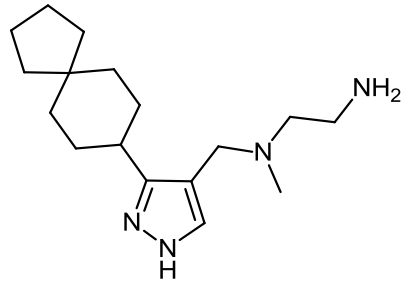


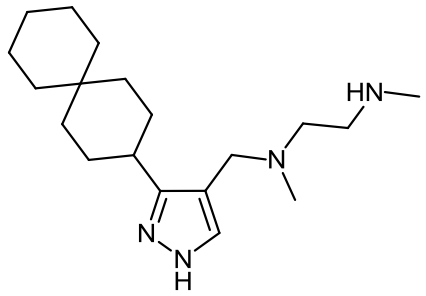
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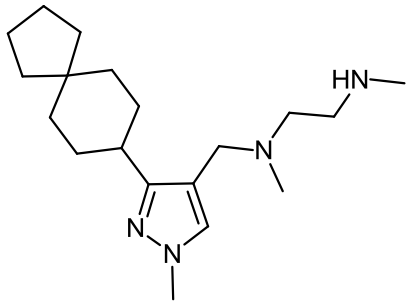
and pharmaceutically acceptable salts thereof.

50. The compound of claim 1, wherein the compound is selected from the group consisting of:

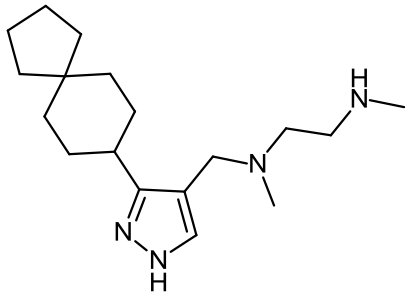
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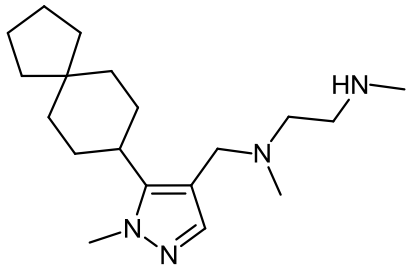
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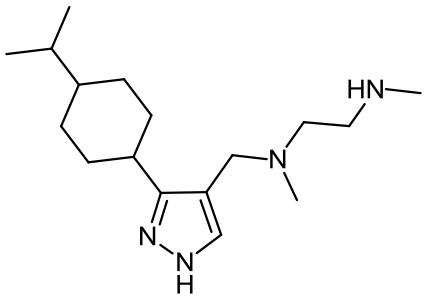
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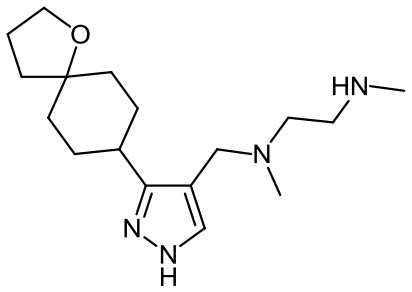
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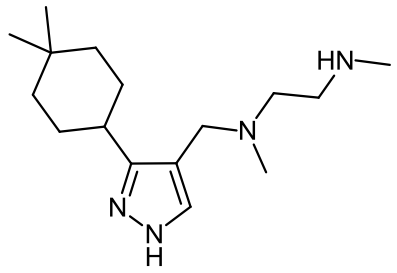
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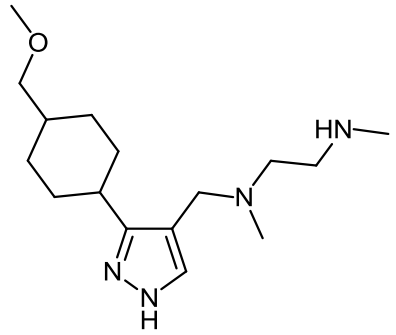
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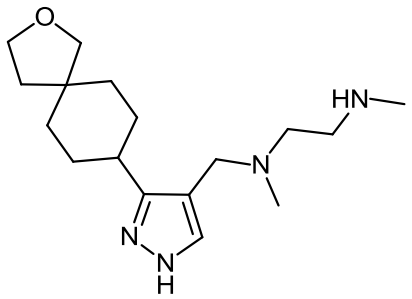
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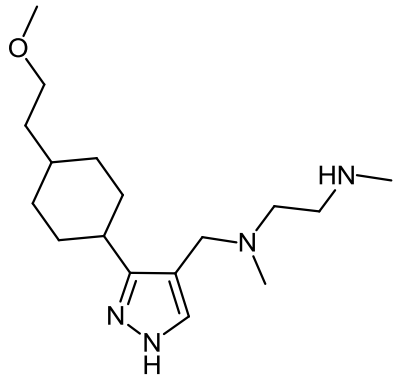
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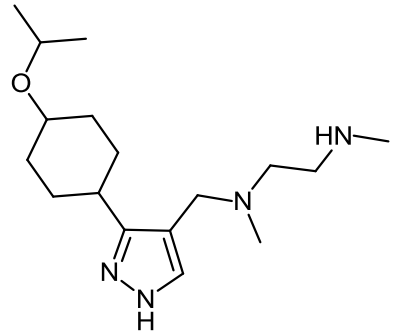
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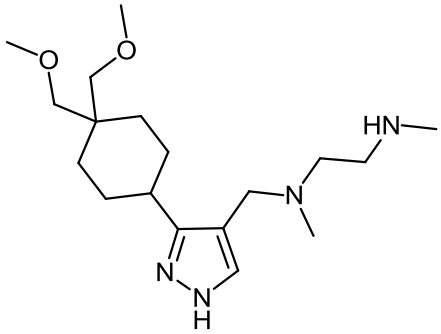
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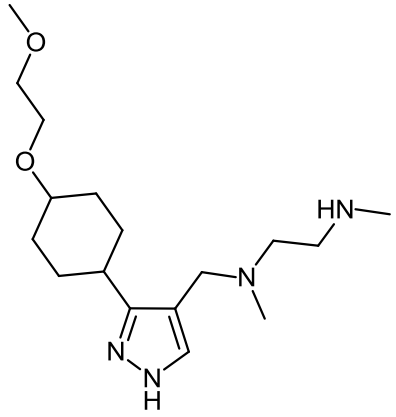
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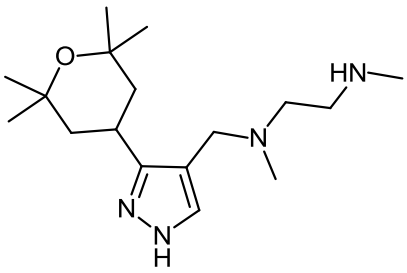
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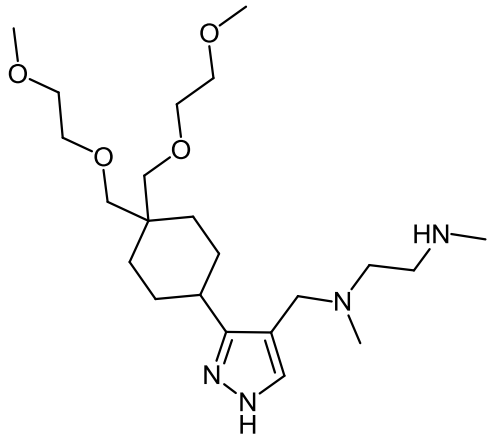
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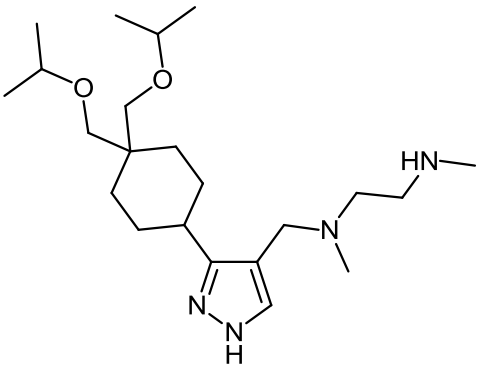
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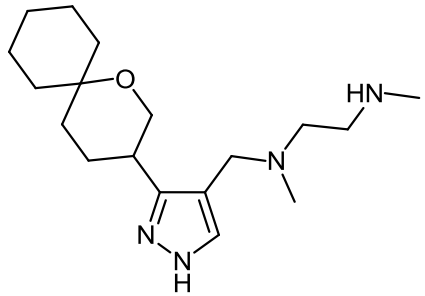
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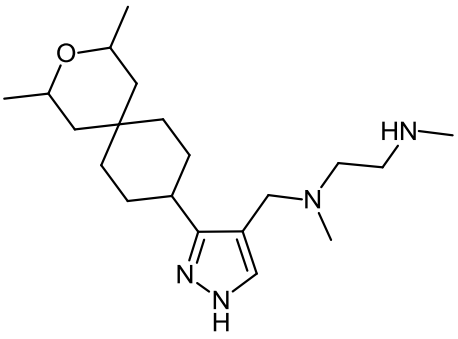
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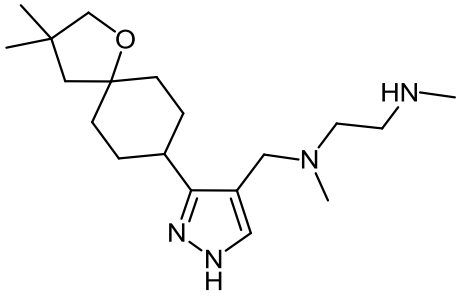
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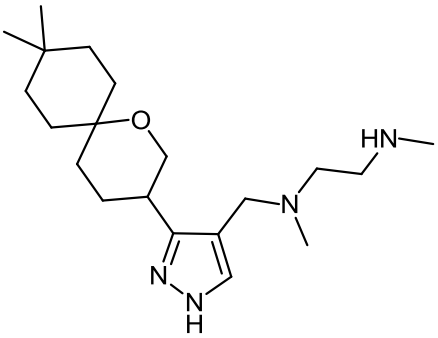
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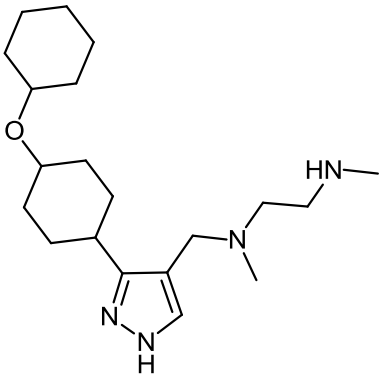
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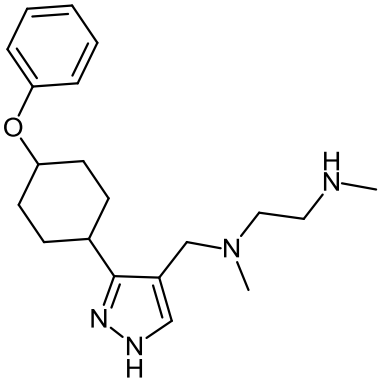
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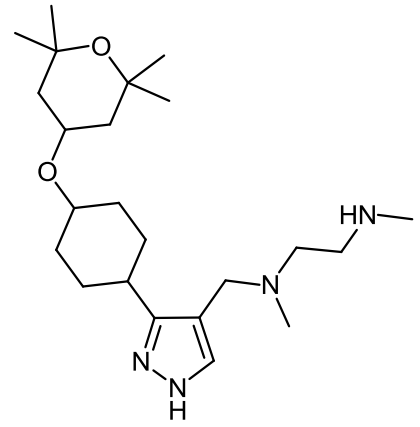
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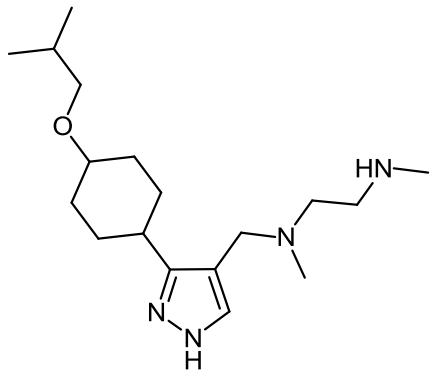
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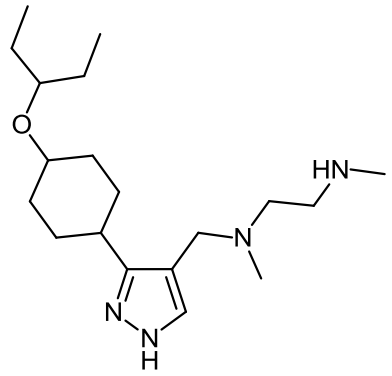
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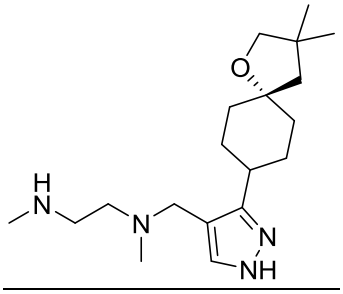
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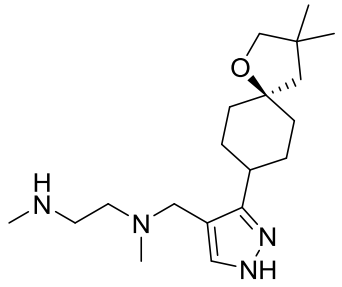
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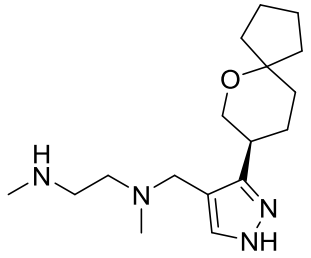
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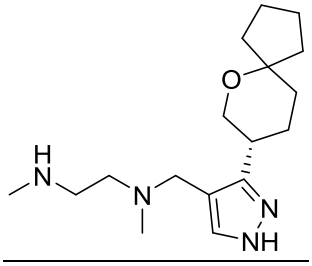
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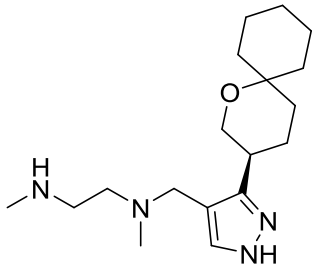
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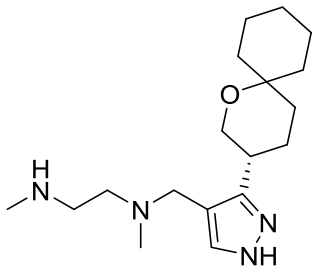
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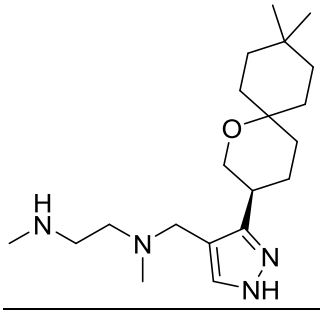
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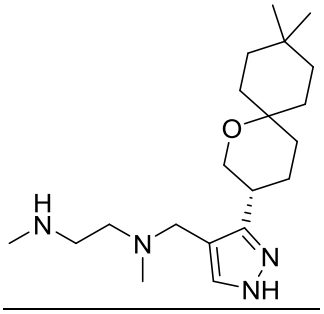
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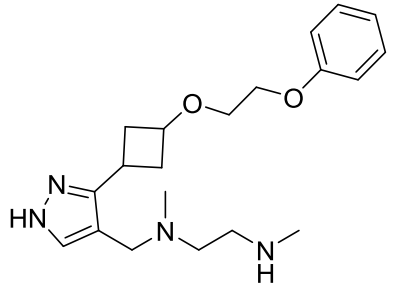
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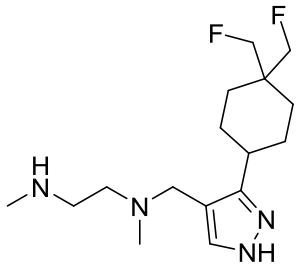
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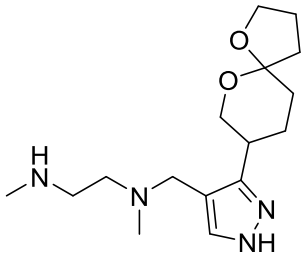
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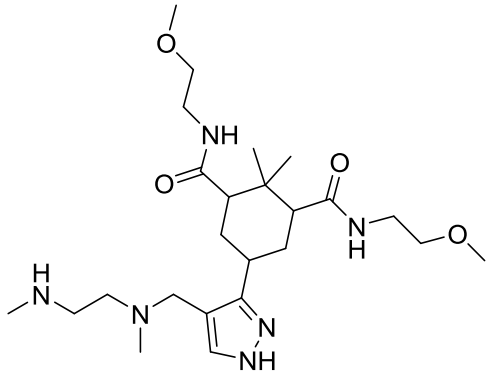
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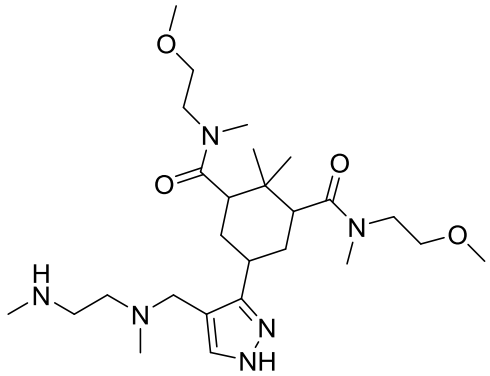
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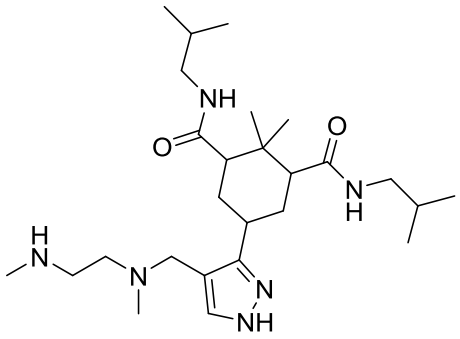
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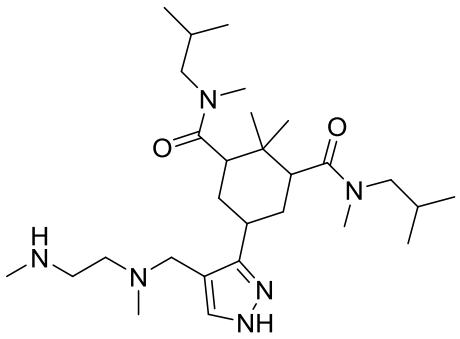
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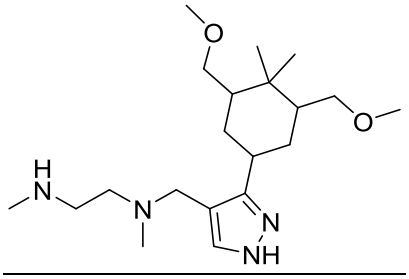
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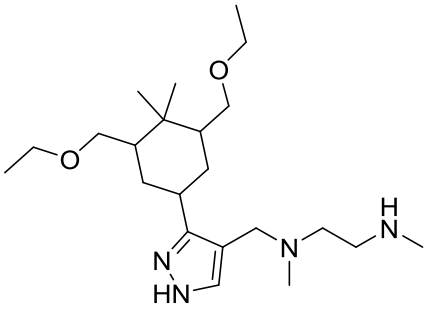
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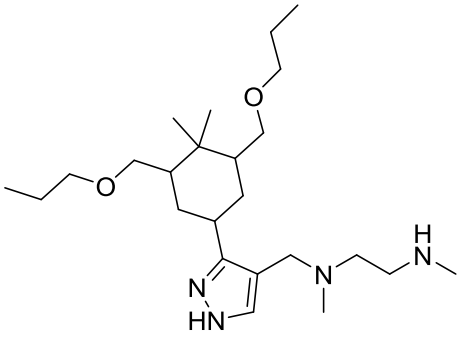
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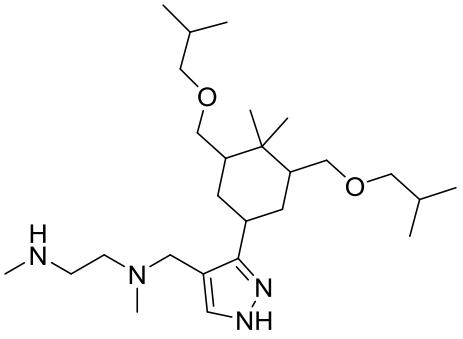
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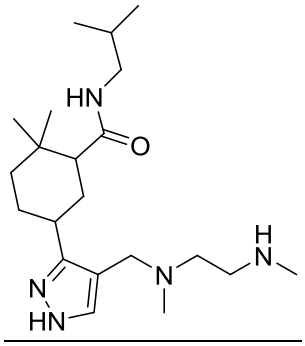
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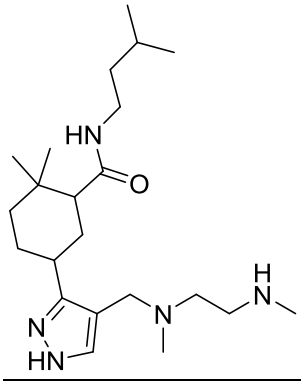
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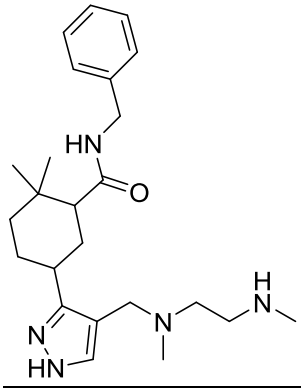
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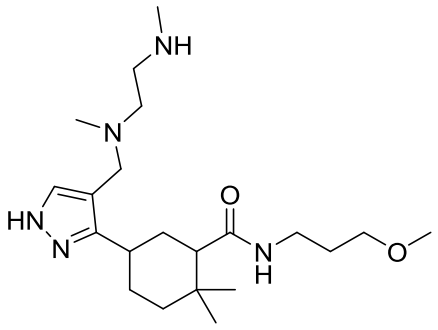
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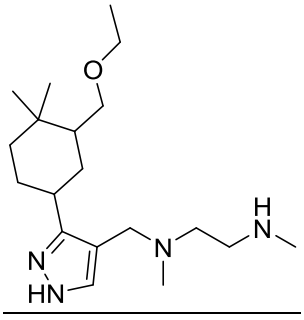
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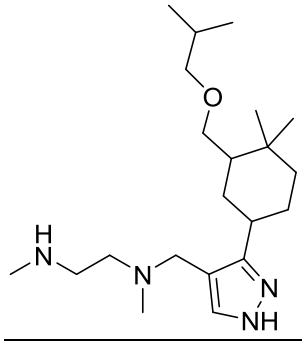
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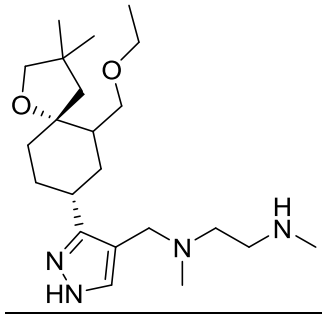
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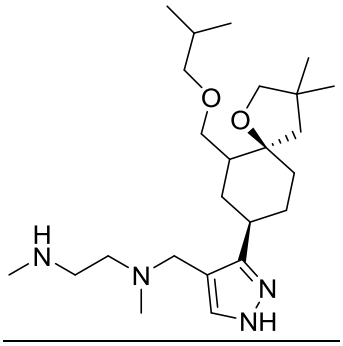
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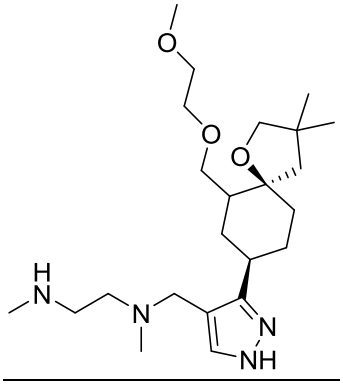
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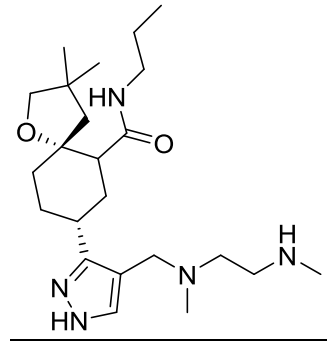
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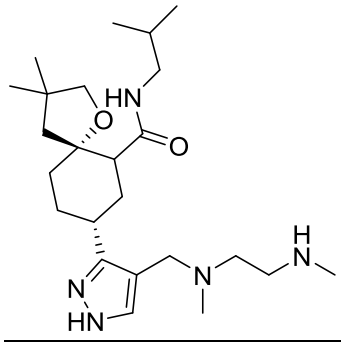
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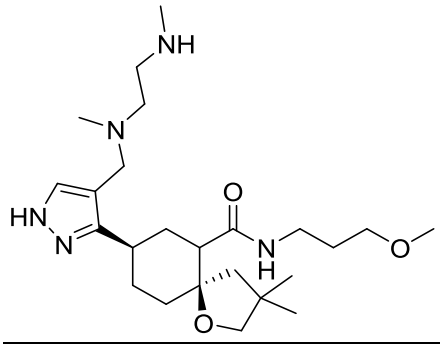
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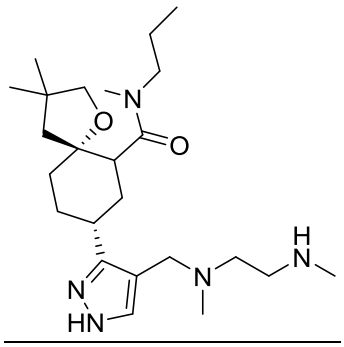
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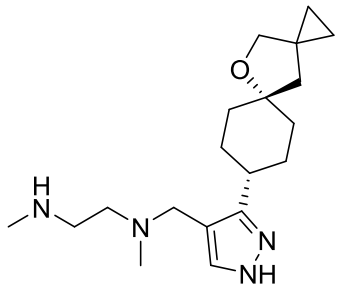
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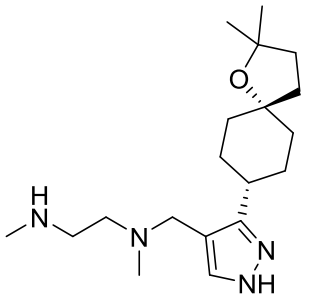
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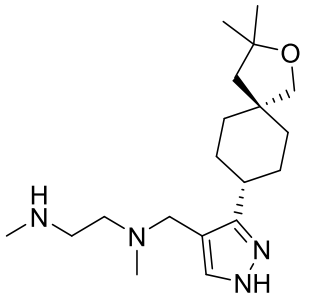
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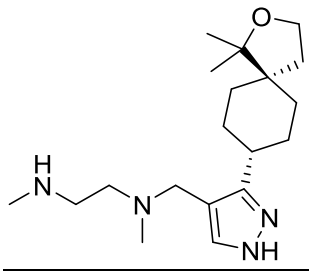
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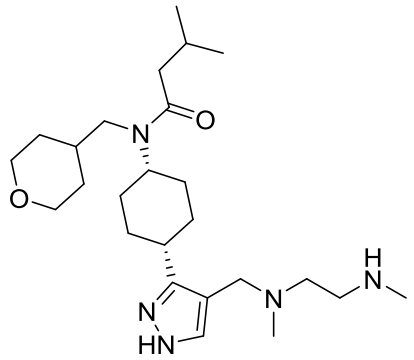
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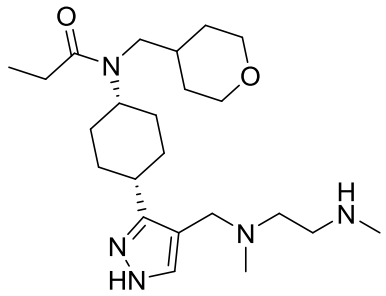
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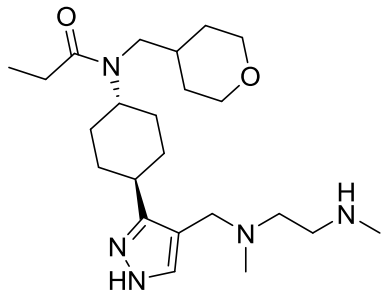
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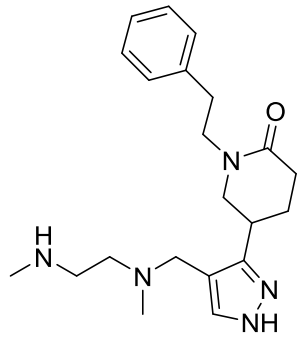
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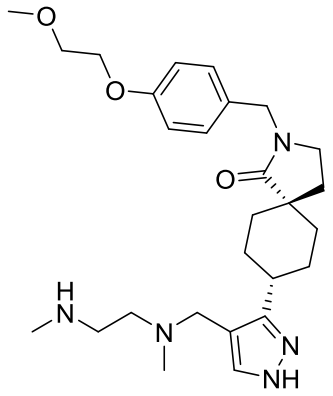
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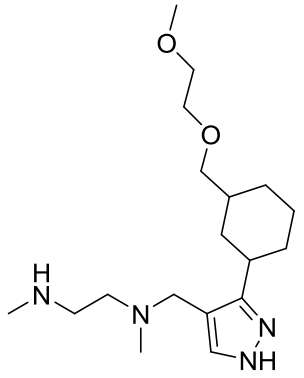
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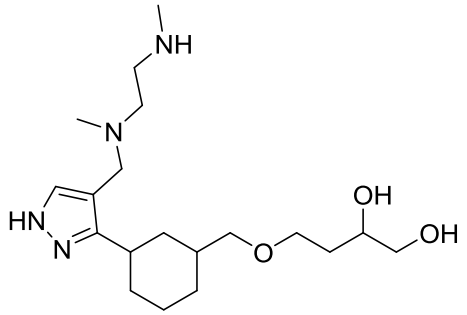
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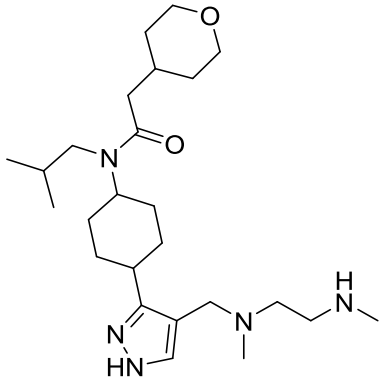
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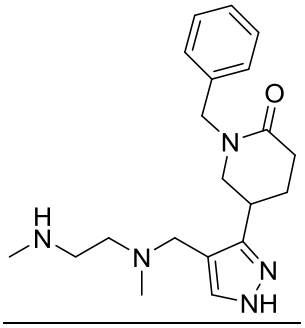
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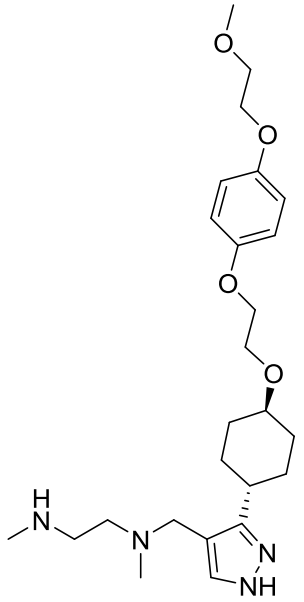
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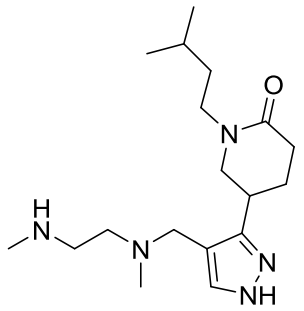
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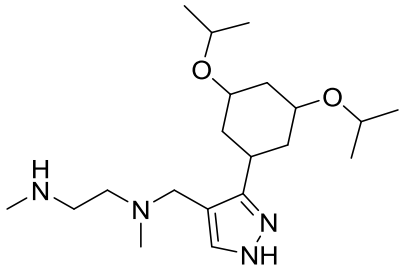
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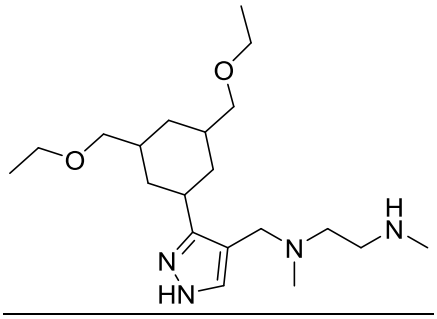
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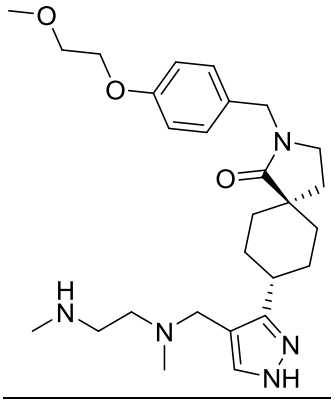
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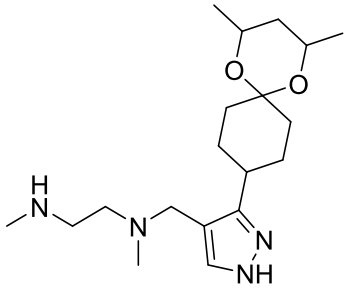
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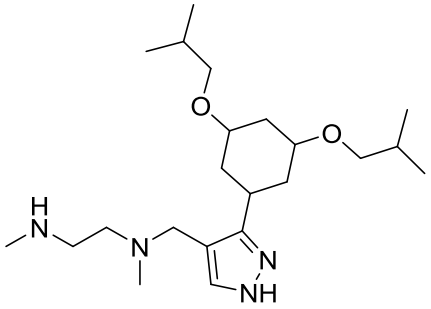
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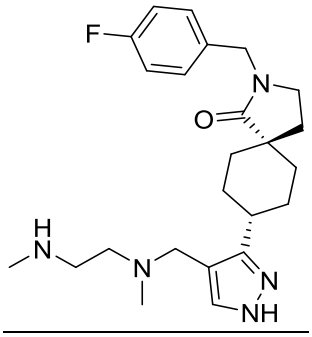
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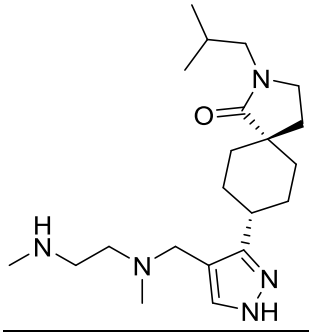
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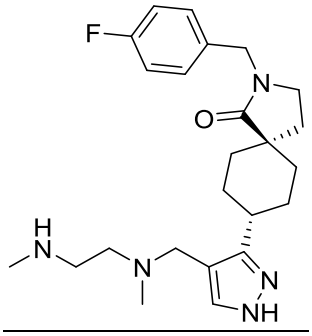
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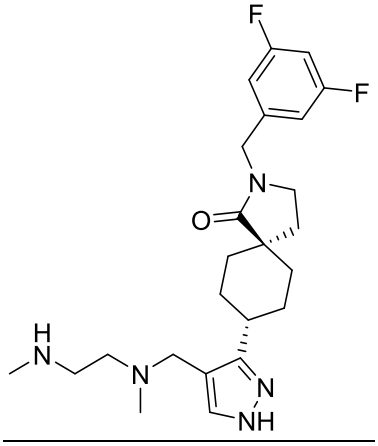
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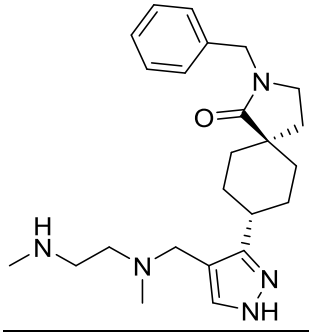
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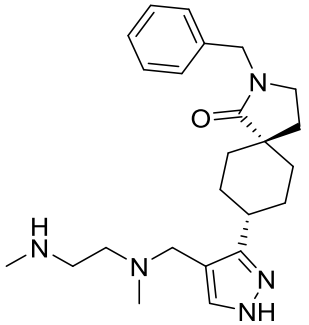
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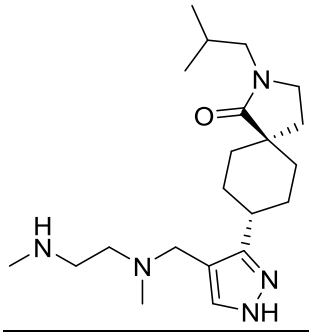
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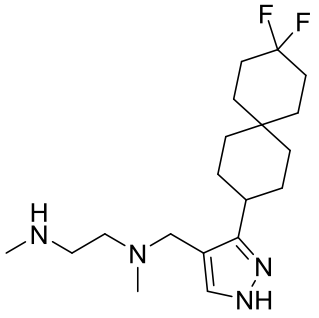
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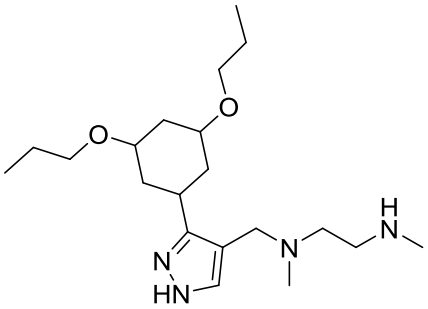
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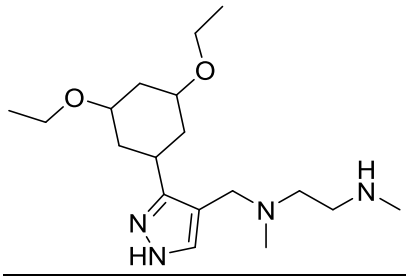
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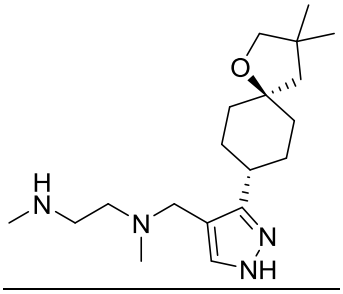
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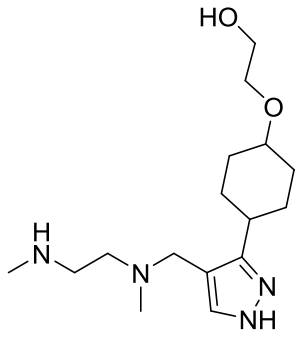
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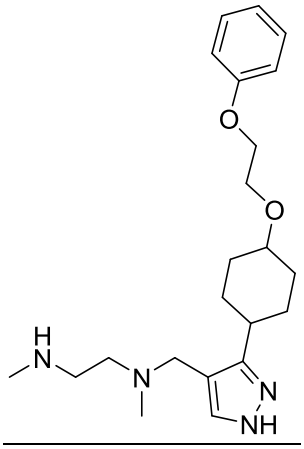
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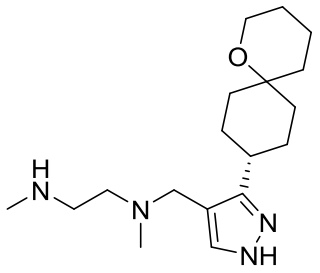
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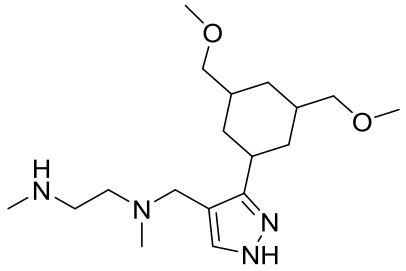
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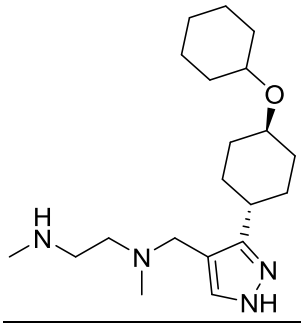
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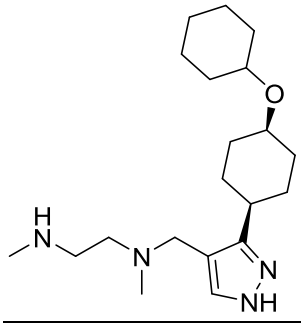
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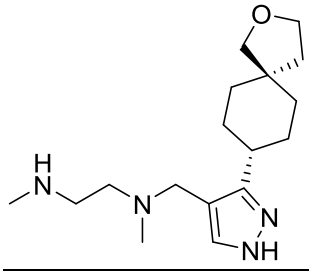
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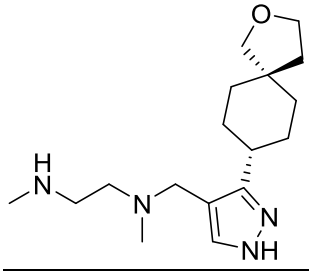
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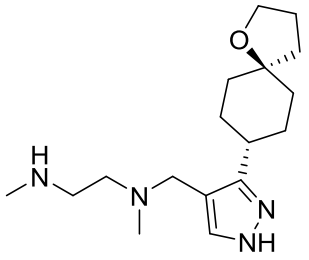
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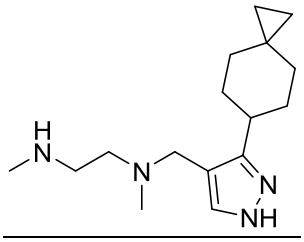
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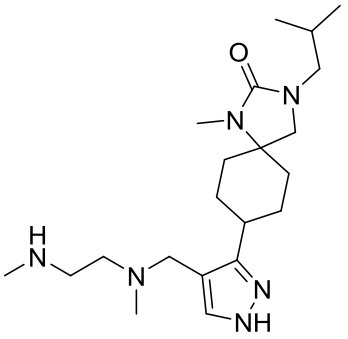
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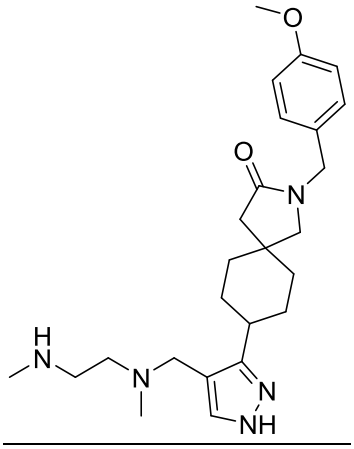
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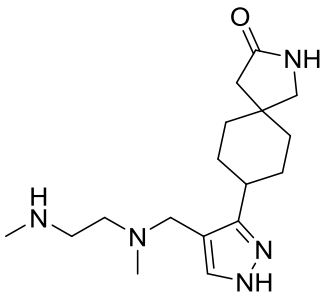
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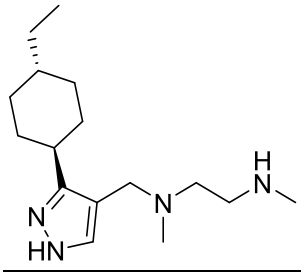
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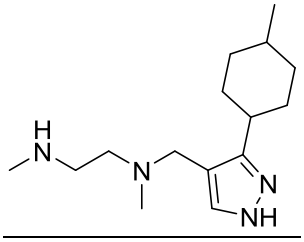
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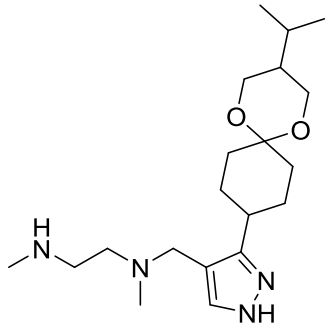
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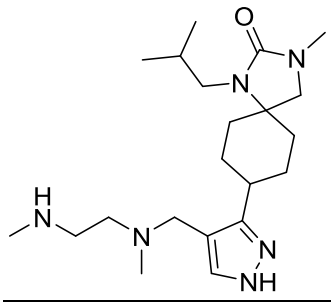
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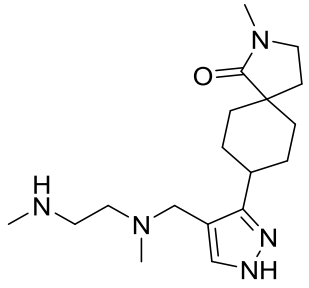
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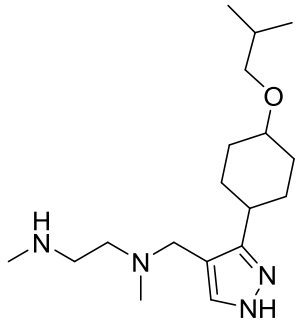
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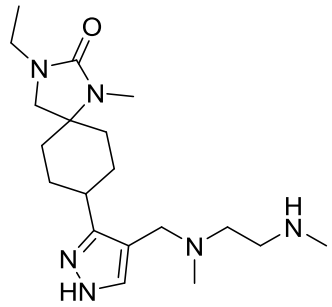
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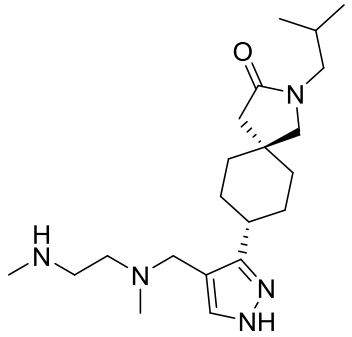
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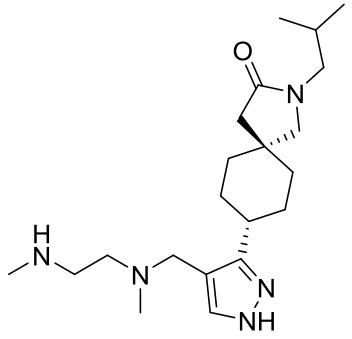
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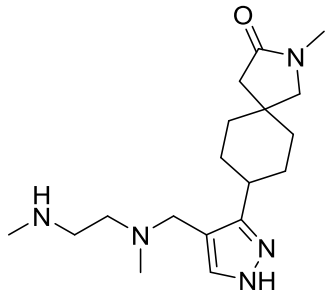
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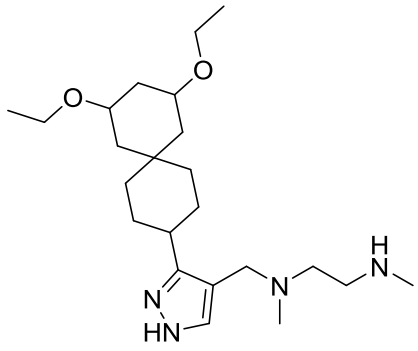
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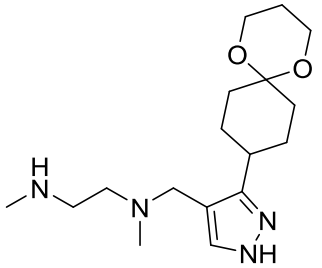
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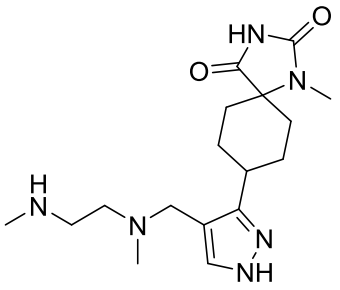
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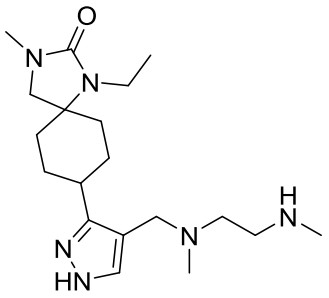
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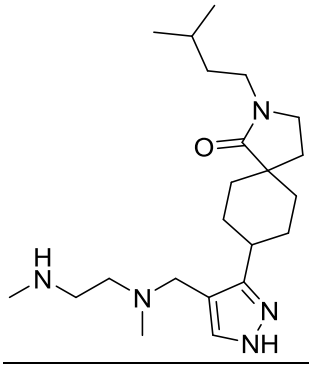
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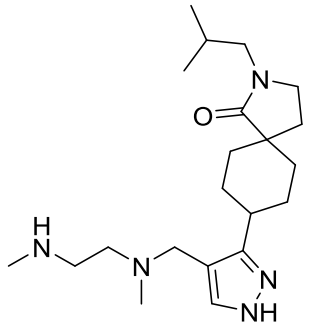
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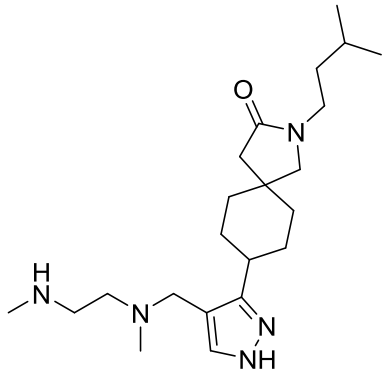
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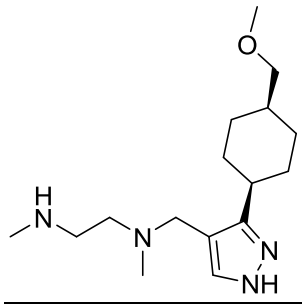
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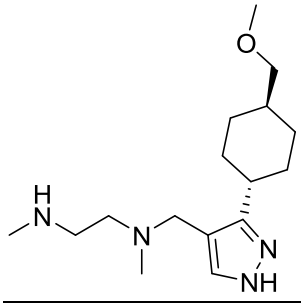
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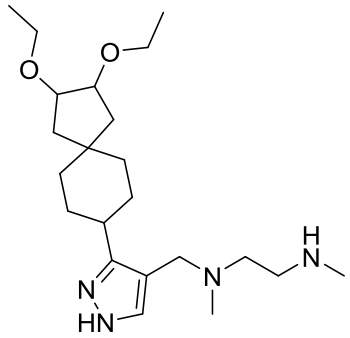
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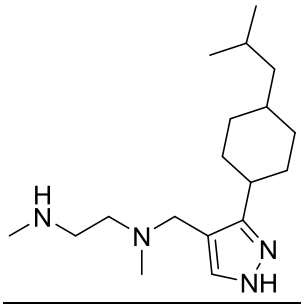
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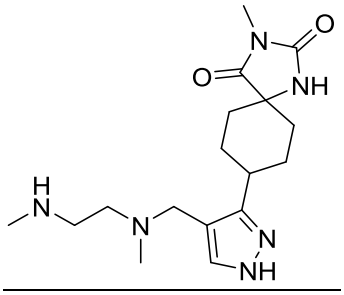
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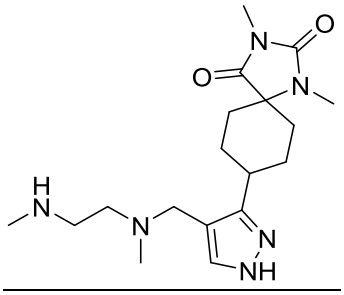
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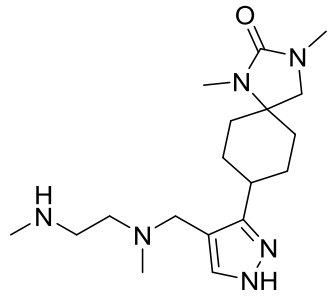
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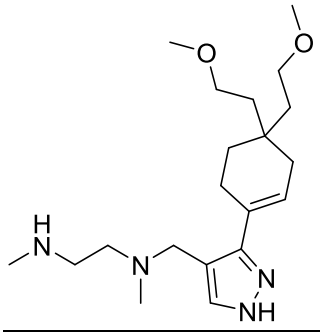
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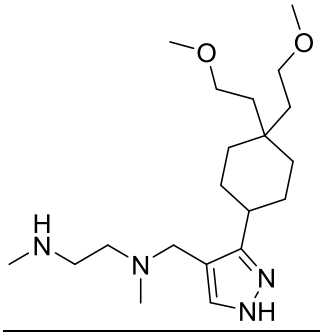
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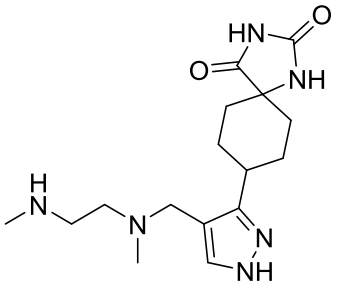
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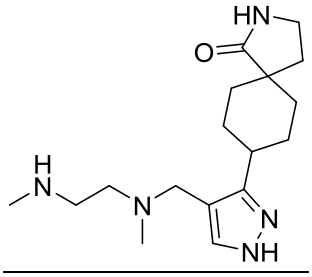
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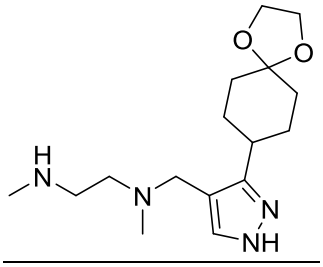
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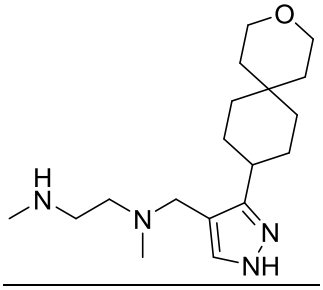
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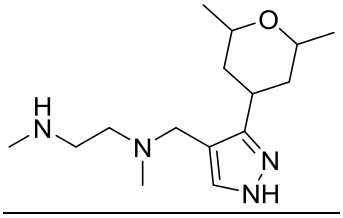
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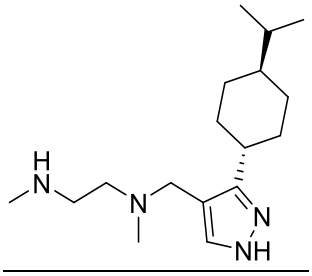
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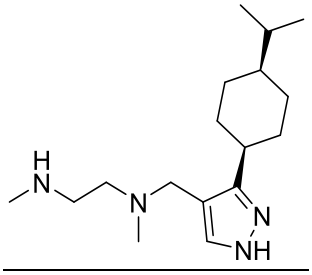
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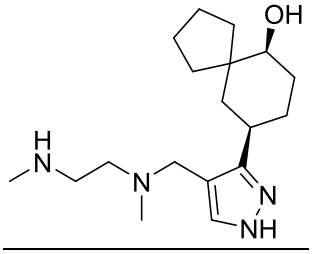
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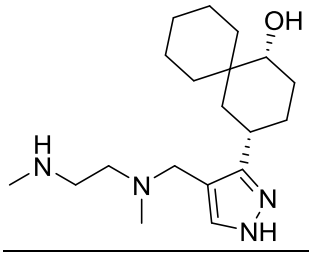
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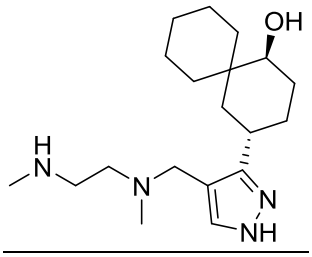
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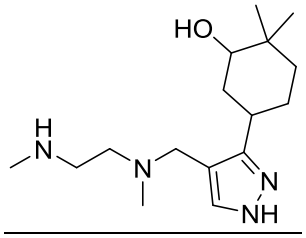
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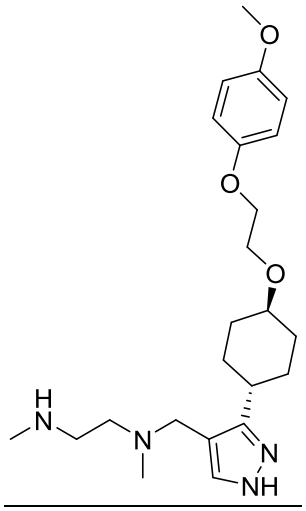
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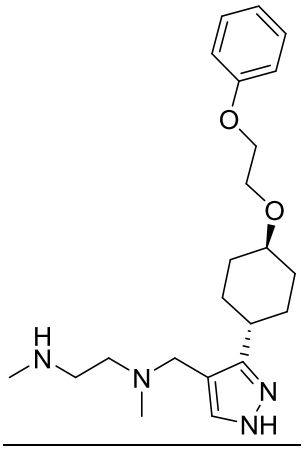
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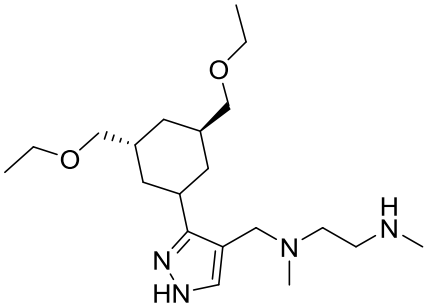
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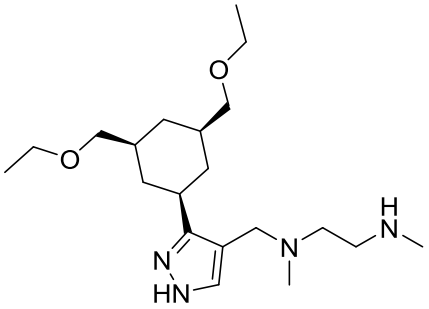
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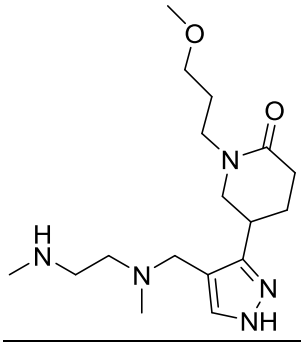
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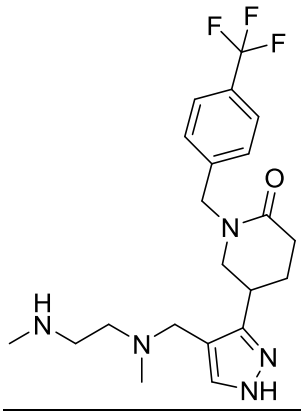
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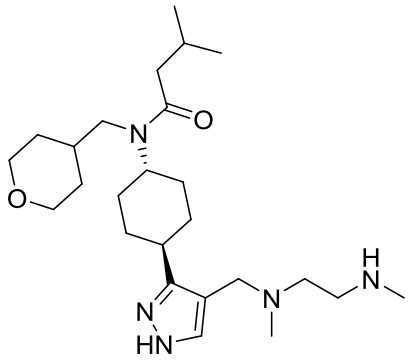
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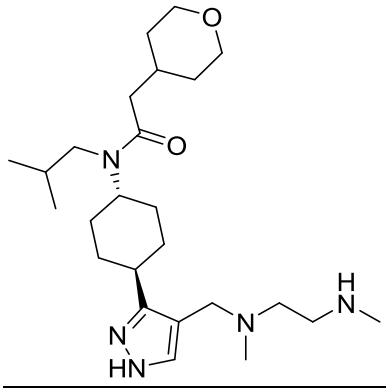
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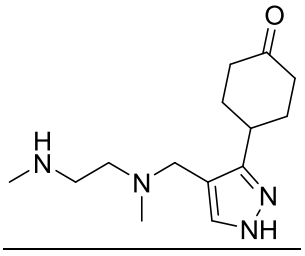
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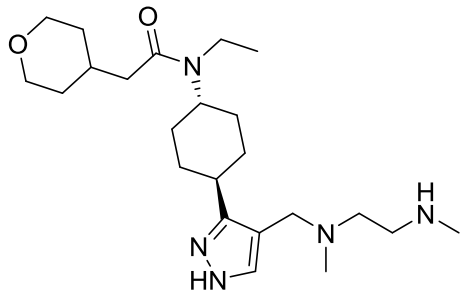
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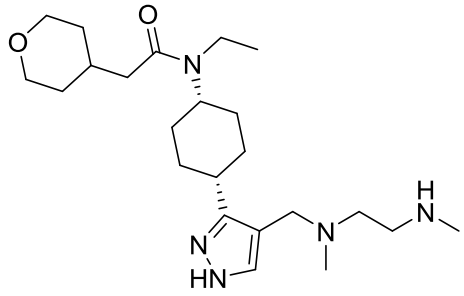
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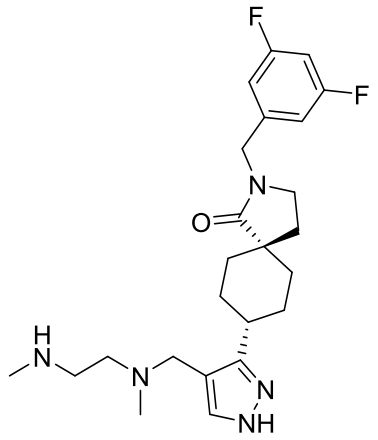
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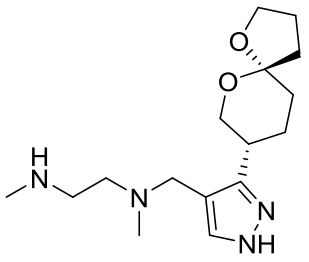
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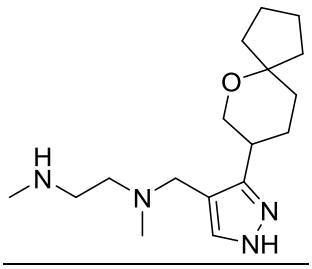
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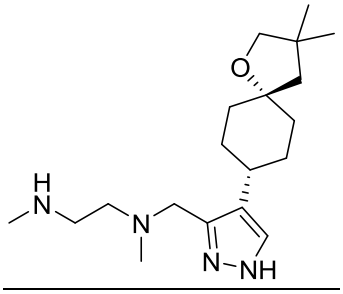
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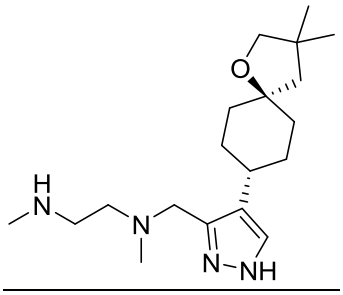
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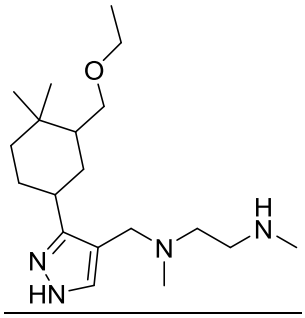
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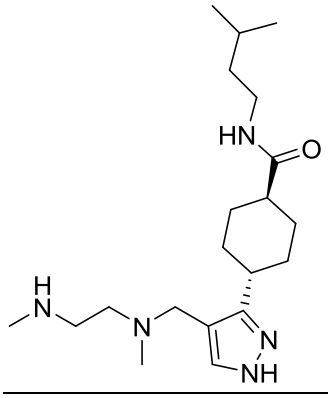
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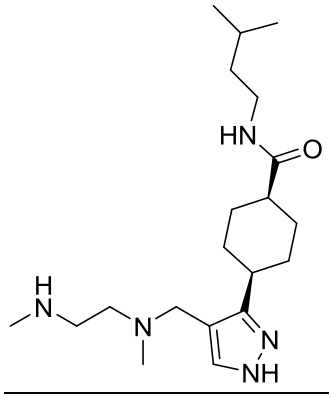
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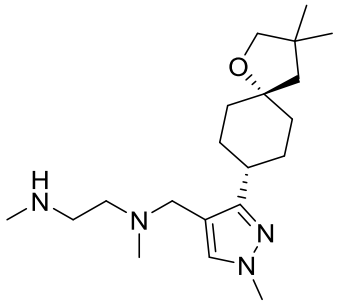
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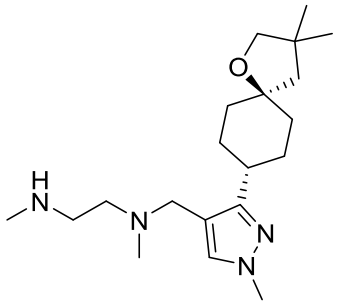
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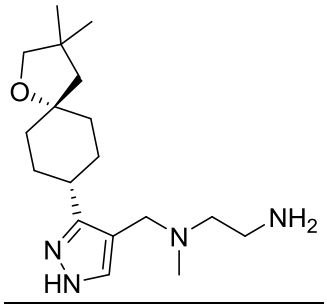
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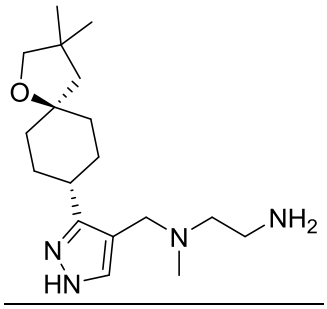
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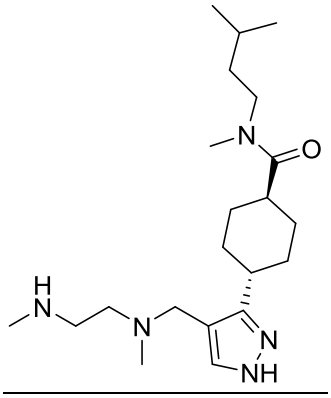
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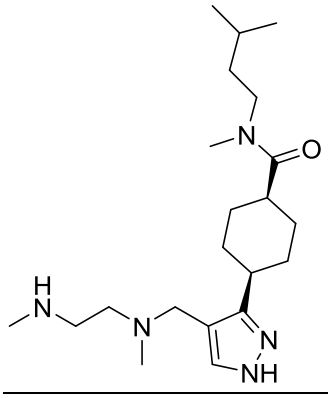
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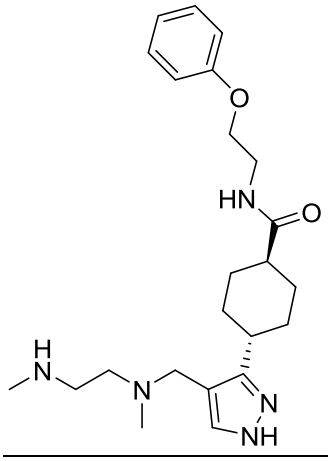
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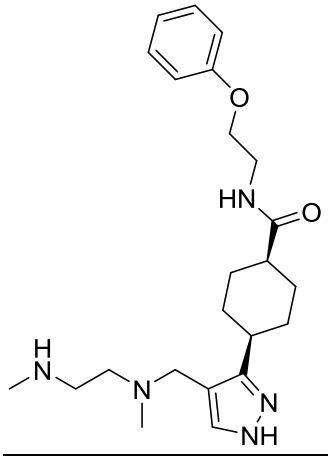
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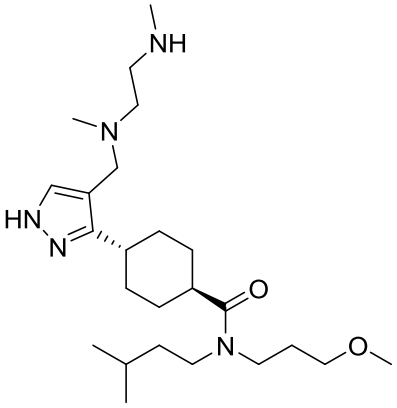
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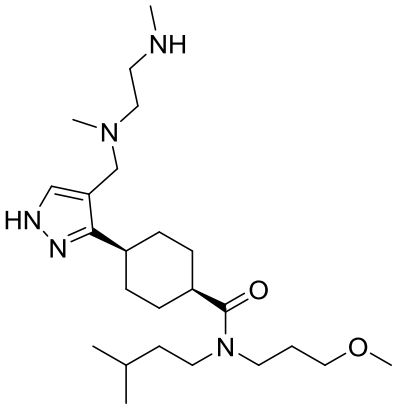
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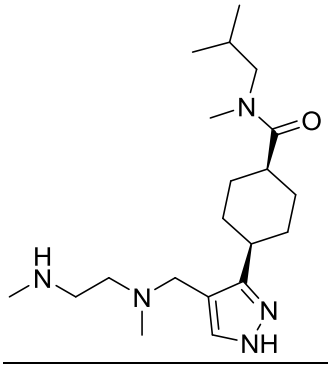
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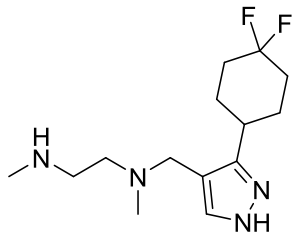
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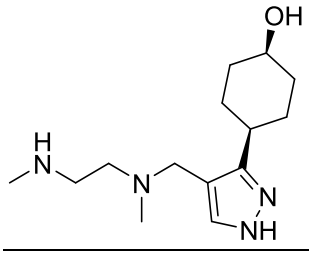
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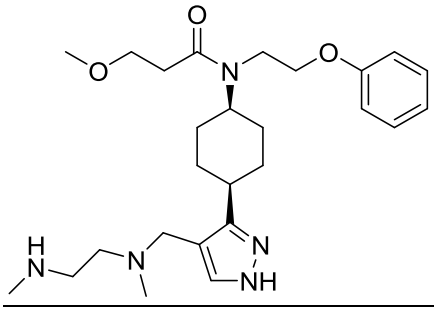
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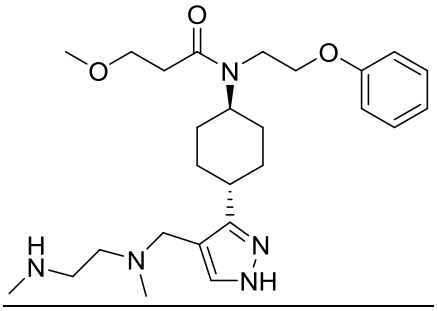
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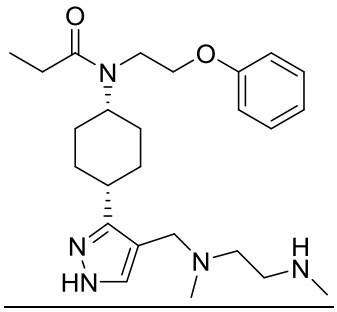
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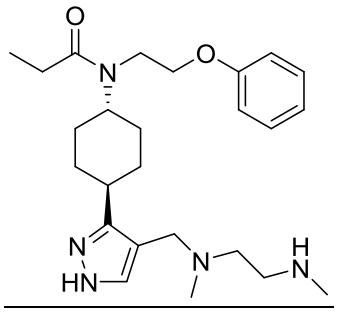
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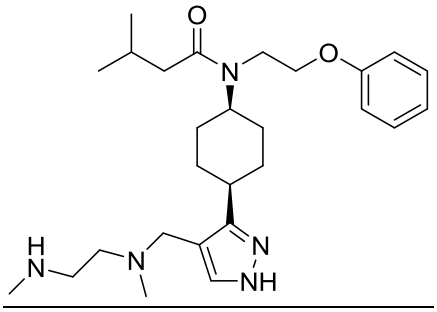
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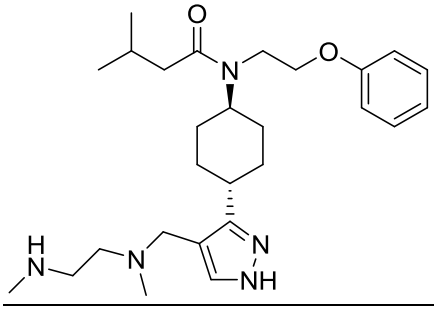
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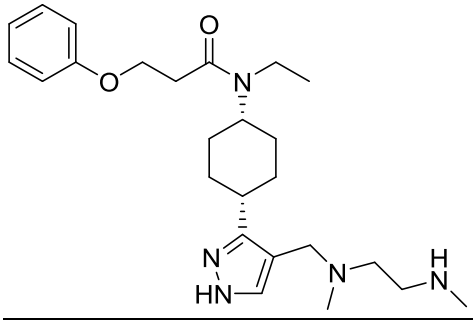
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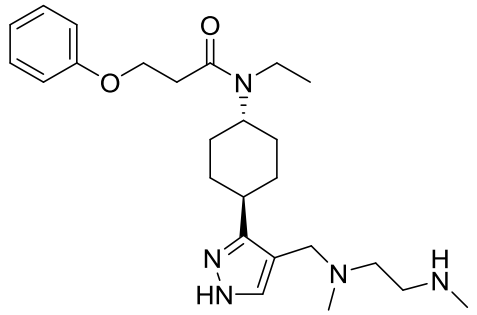
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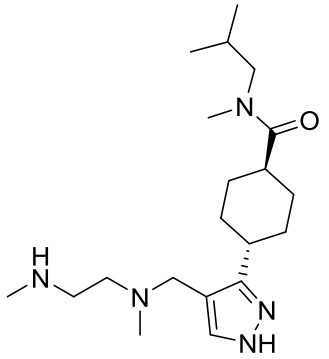
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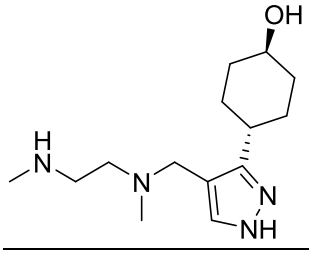
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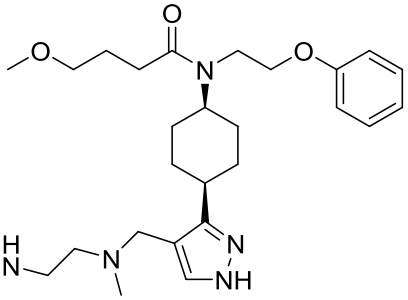
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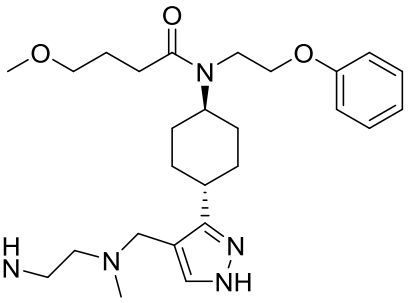
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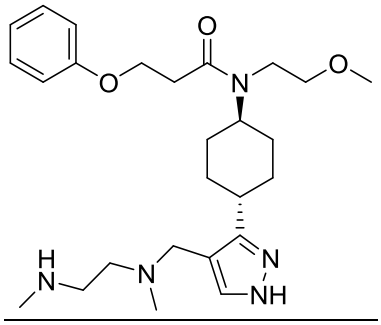
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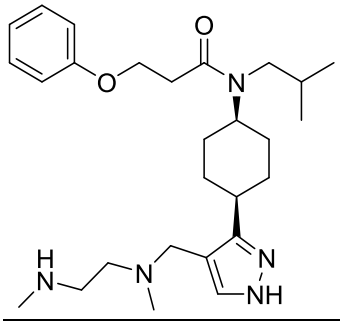
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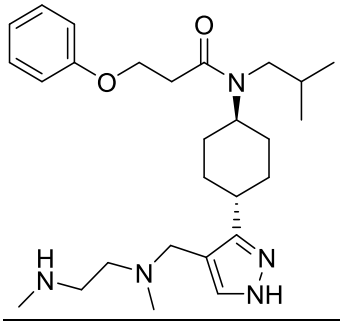
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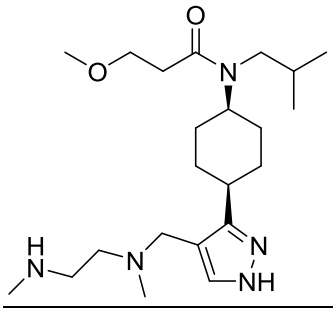
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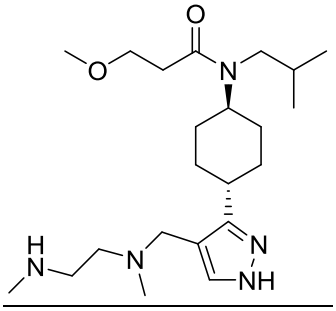
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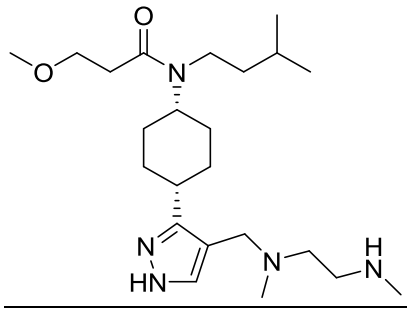
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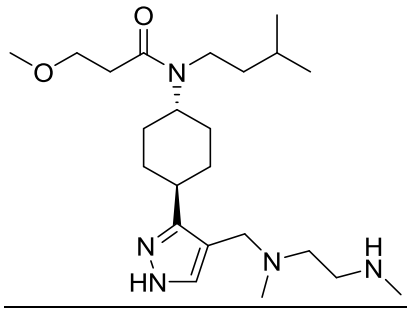
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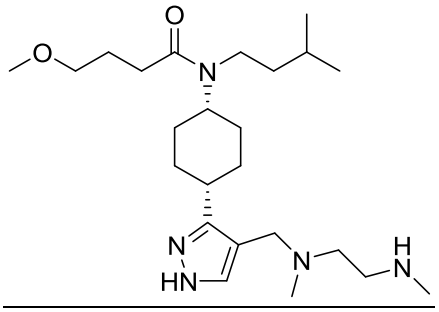
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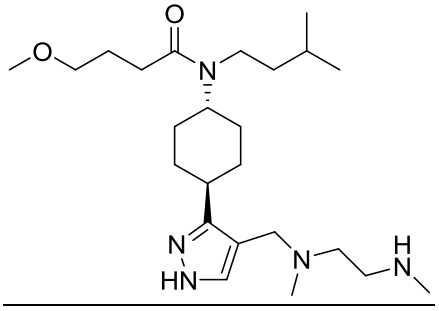
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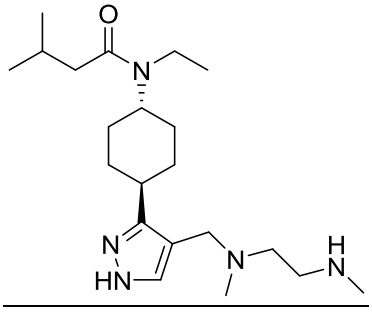
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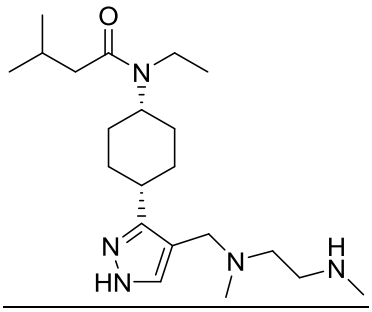
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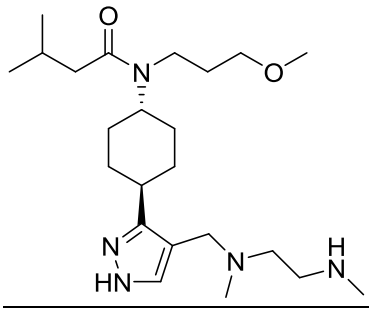
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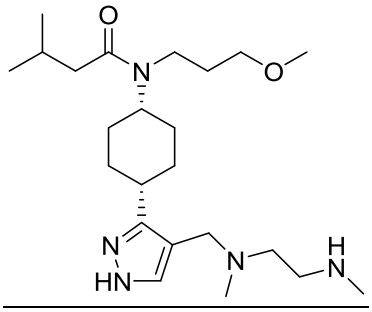
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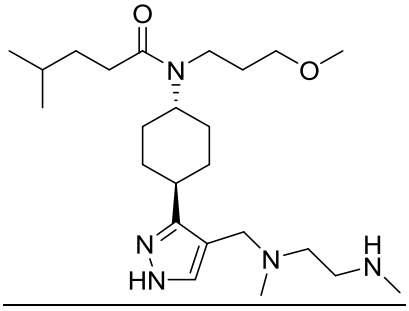
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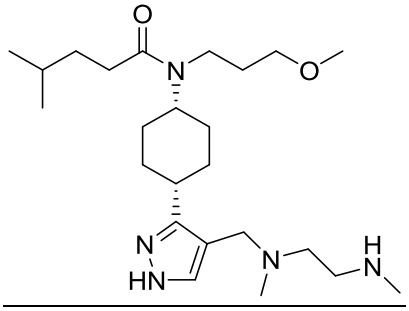
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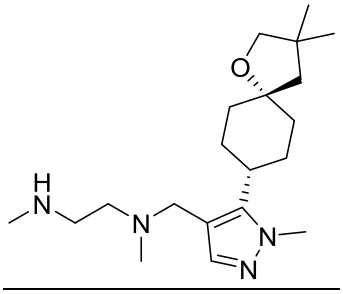
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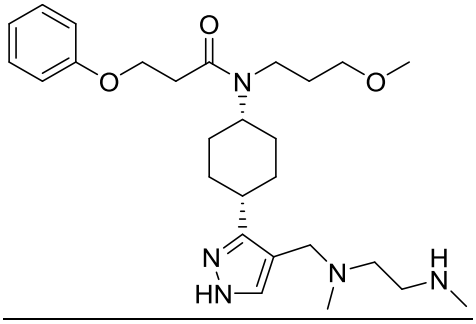
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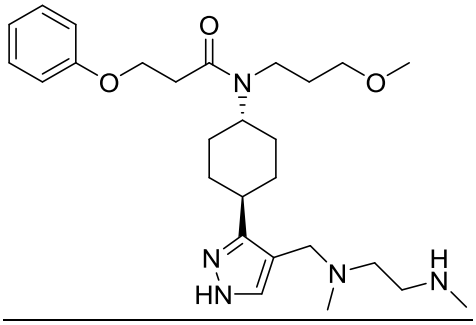
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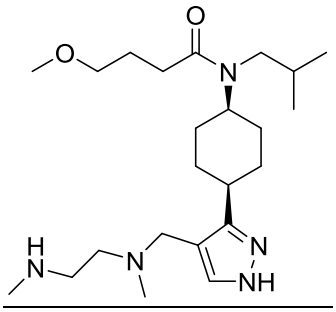
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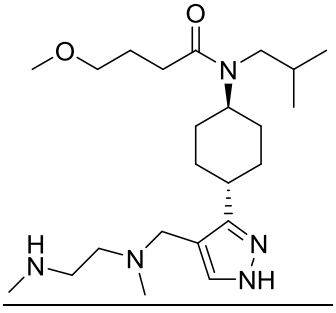
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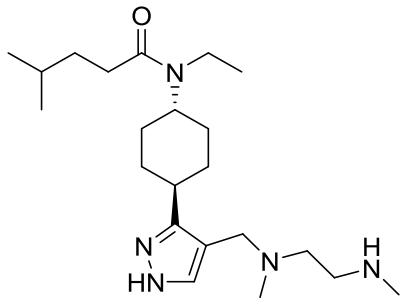
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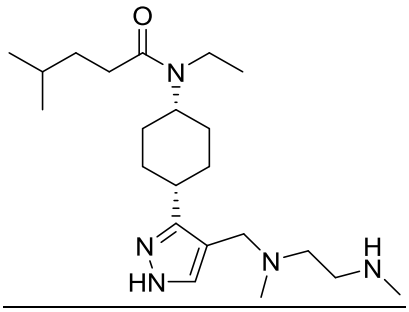
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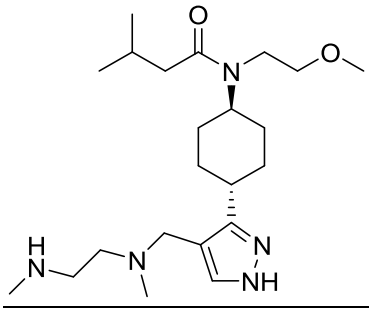
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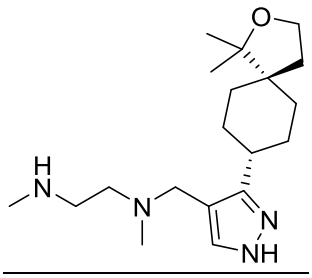
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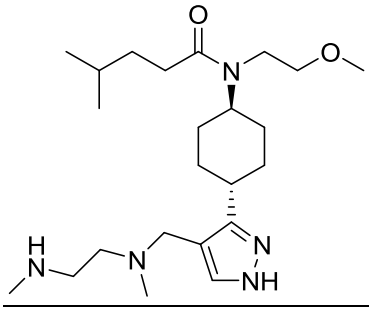
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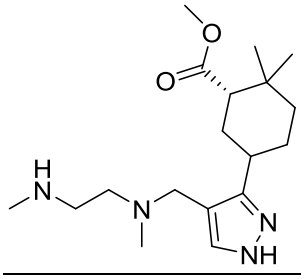
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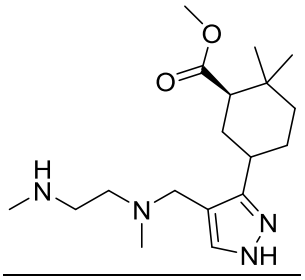
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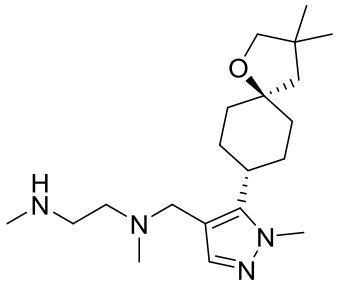
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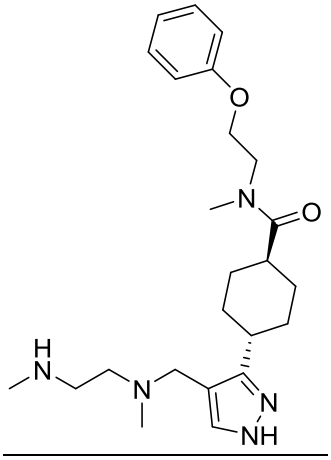
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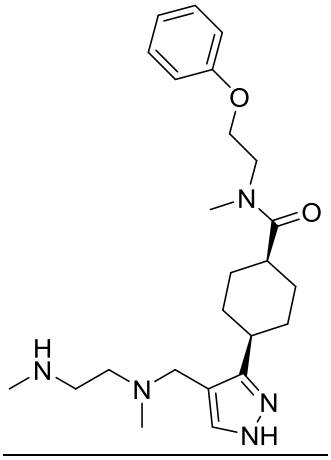
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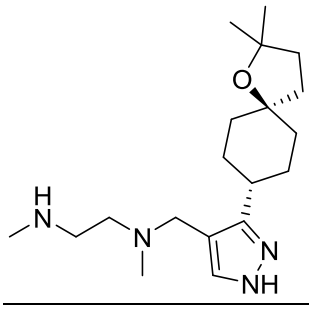
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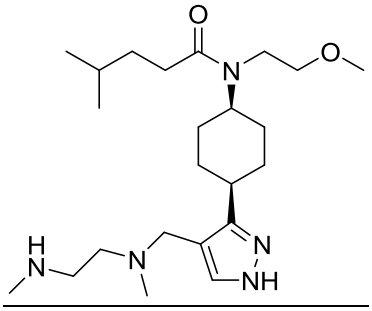
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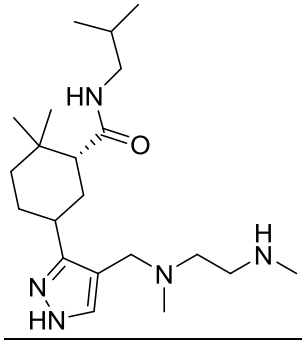
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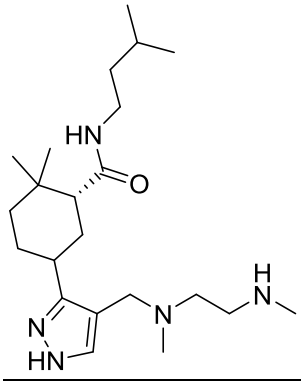
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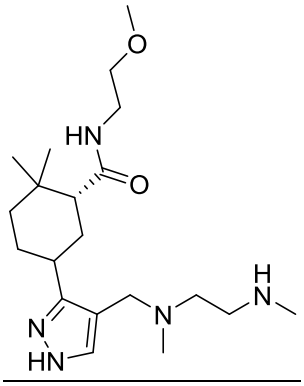
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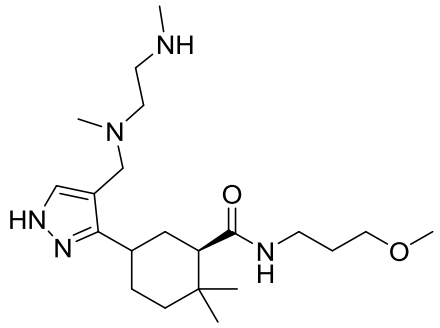
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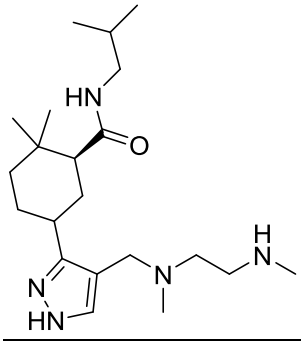
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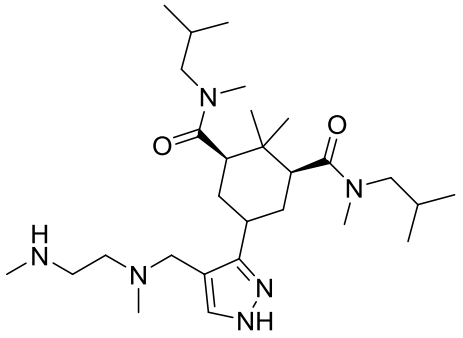
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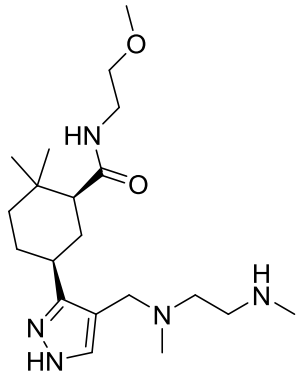
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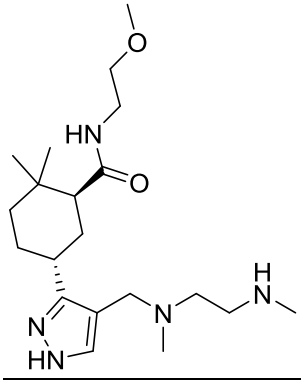
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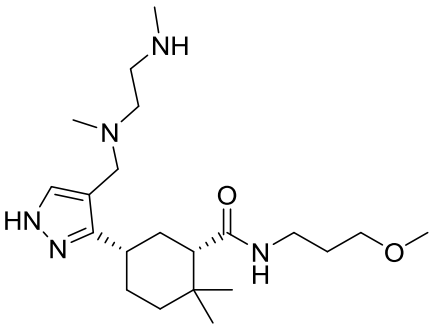
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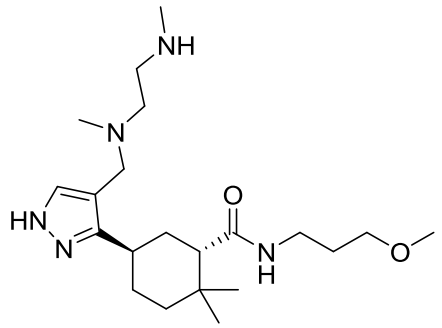
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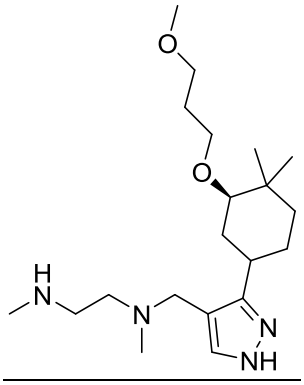
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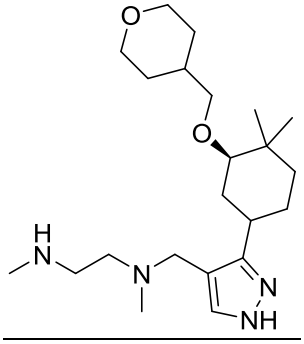
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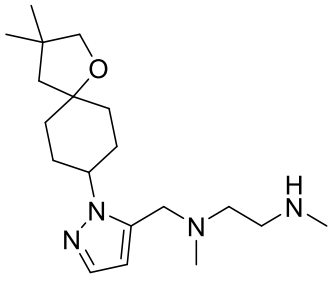
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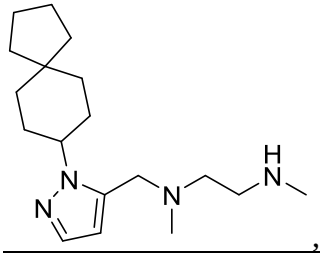
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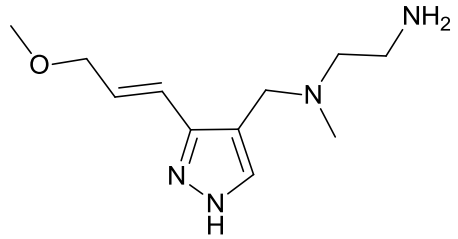
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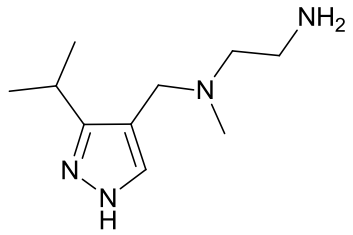


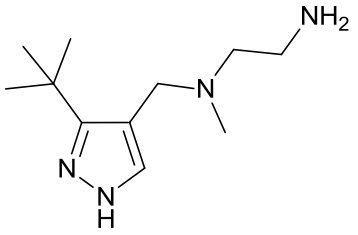
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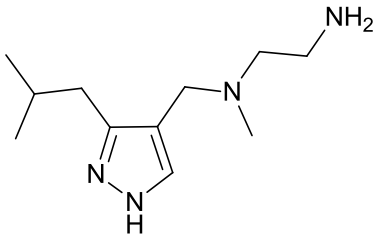
and pharmaceutically acceptable salts thereof.

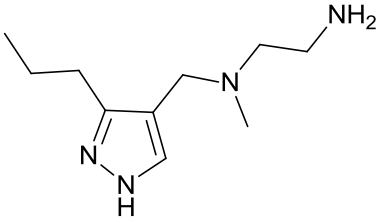
51. A compound selected from the group consisting of:

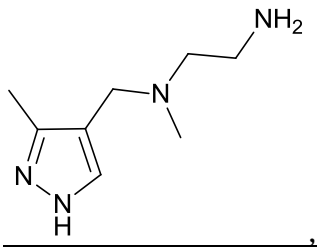
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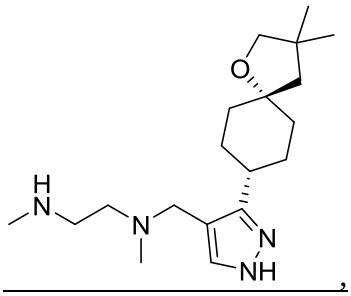
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and pharmaceutically acceptable salts thereof.

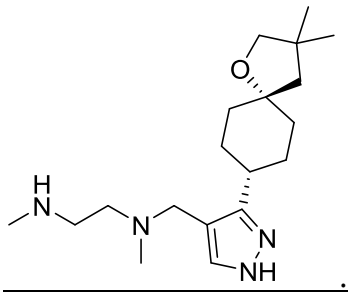
52. A compound of formula:



,

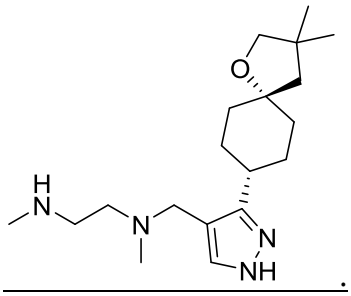
or a pharmaceutically acceptable salt thereof.

53. The compound of claim 52, wherein the compound is:



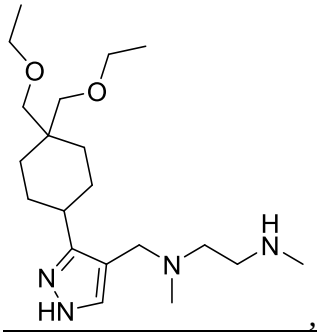
.

54. The compound of claim 52, wherein the compound is a pharmaceutically acceptable salt of:



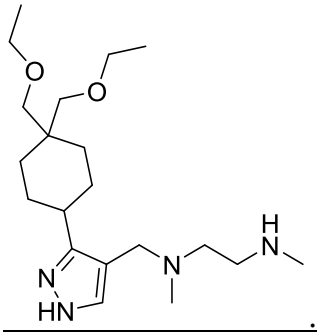
.

55. A compound of formula:

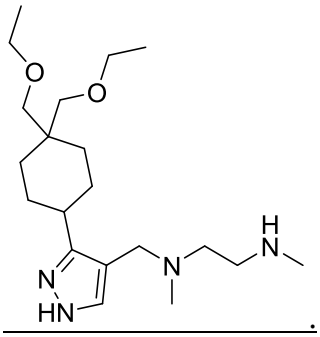


or a pharmaceutically acceptable salt thereof.

56. The compound of claim 55, wherein the compound is:



57. The compound of claim 55, wherein the compound is a pharmaceutically acceptable salt of:



58. A pharmaceutical composition comprising a compound of any one of claims 1-51, and a pharmaceutically acceptable excipient.

59. A pharmaceutical composition comprising a compound of claim 52, and a pharmaceutically acceptable excipient.

60. A pharmaceutical composition comprising a compound of claim 53, and a pharmaceutically acceptable excipient.

61. A pharmaceutical composition comprising a compound of claim 54, and a pharmaceutically acceptable excipient.

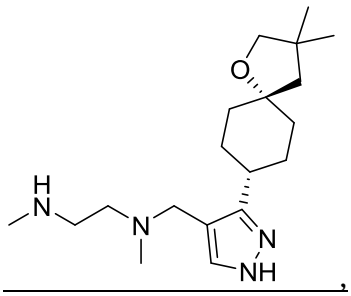
62. A pharmaceutical composition comprising a compound of claim 55, and a pharmaceutically acceptable excipient.

63. A pharmaceutical composition comprising a compound of claim 56, and a pharmaceutically acceptable excipient.

64. A pharmaceutical composition comprising a compound of claim 57, and a pharmaceutically acceptable excipient.

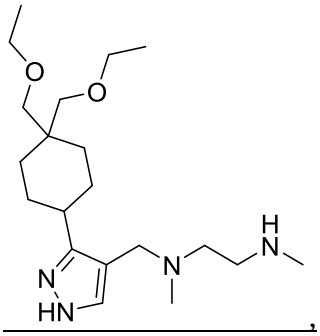
65. A kit or packaged pharmaceutical comprising a compound of any one of claims 1-57, and instructions for use thereof.

66. The kit or packaged pharmaceutical of claim 65, wherein the compound is



or a pharmaceutically acceptable salt thereof.

67. The kit or packaged pharmaceutical of claim 65, wherein the compound is



or a pharmaceutically acceptable salt thereof.

68. Use of a compound of any one of claims 1-57 in the preparation of a medicament for inhibiting an arginine methyltransferase (RMT), wherein inhibiting the RMT comprises contacting a cell with an effective amount of the compound.

69. The use of claim 68, wherein the arginine methyl transferase is PRMT1.

70. The use of claim 68, wherein the arginine methyl transferase is PRMT6.

71. The use of claim 68, wherein the arginine methyl transferase is PRMT3.

72. The use of claim 68, wherein the arginine methyl transferase is PRMT8.

73. The use of claim 68, wherein the arginine methyl transferase is CARM1.

74. Use of a compound of any one of claims 1-57 in the preparation of a medicament for modulating gene expression, wherein modulating gene expression comprises contacting a cell with an effective amount of the compound.

75. Use of a compound of any one of claims 1-57 in the preparation of a medicament for modulating transcription, wherein modulating transcription comprises contacting a cell with an effective amount of the compound.

76. The use of any one of claims 68-75, wherein the cell is in vitro.

77. The use of any one of claims 68-75, wherein the cell is in a subject.

78. Use of a compound of any one of claims 1-57 in the preparation of a medicament for treating a RMT-mediated disorder.

79. The use of claim 78, wherein the RMT-mediated disorder is a PRMT1-mediated disorder.

80. The use of claim 78, wherein the RMT-mediated disorder is a PRMT6-mediated disorder.

81. The use of claim 78, wherein the RMT-mediated disorder is a PRMT3-mediated disorder.

82. The use of claim 78, wherein the RMT-mediated disorder is a PRMT8-mediated disorder.

83. The use of claim 78, wherein the RMT-mediated disorder is a CARM1-mediated disorder.

84. The use of claim 78, wherein the disorder is a proliferative disorder.

85. The use of claim 84, wherein the disorder is cancer.

86. The use of claim 78, wherein the disorder is a neurological disorder.

87. The use of claim 86, wherein the disorder is amyotrophic lateral sclerosis.

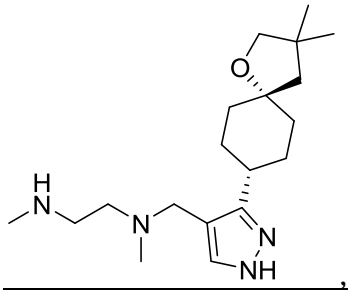
88. The use of claim 78, wherein the disorder is a muscular dystrophy.

89. The use of claim 78, wherein the disorder is an autoimmune disorder.

90. The use of claim 78, wherein the disorder is a vascular disorder.

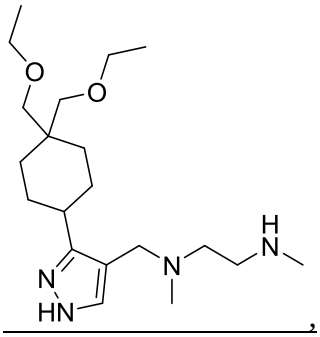
91. The use of claim 78, wherein the disorder is a metabolic disorder.

92. The use of any one of claims 68-91, wherein the compound is



or a pharmaceutically acceptable salt thereof.

93. The use of any one of claims 68-91, wherein the compound is



or a pharmaceutically acceptable salt thereof.