

(I)

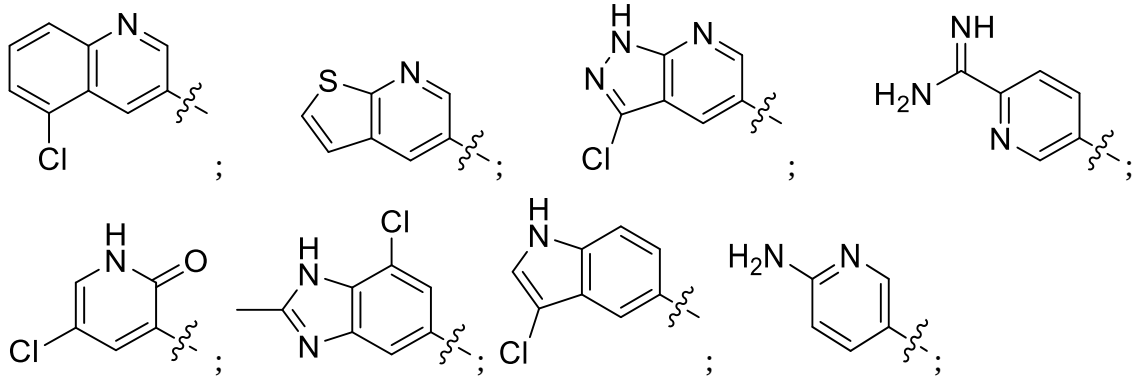
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

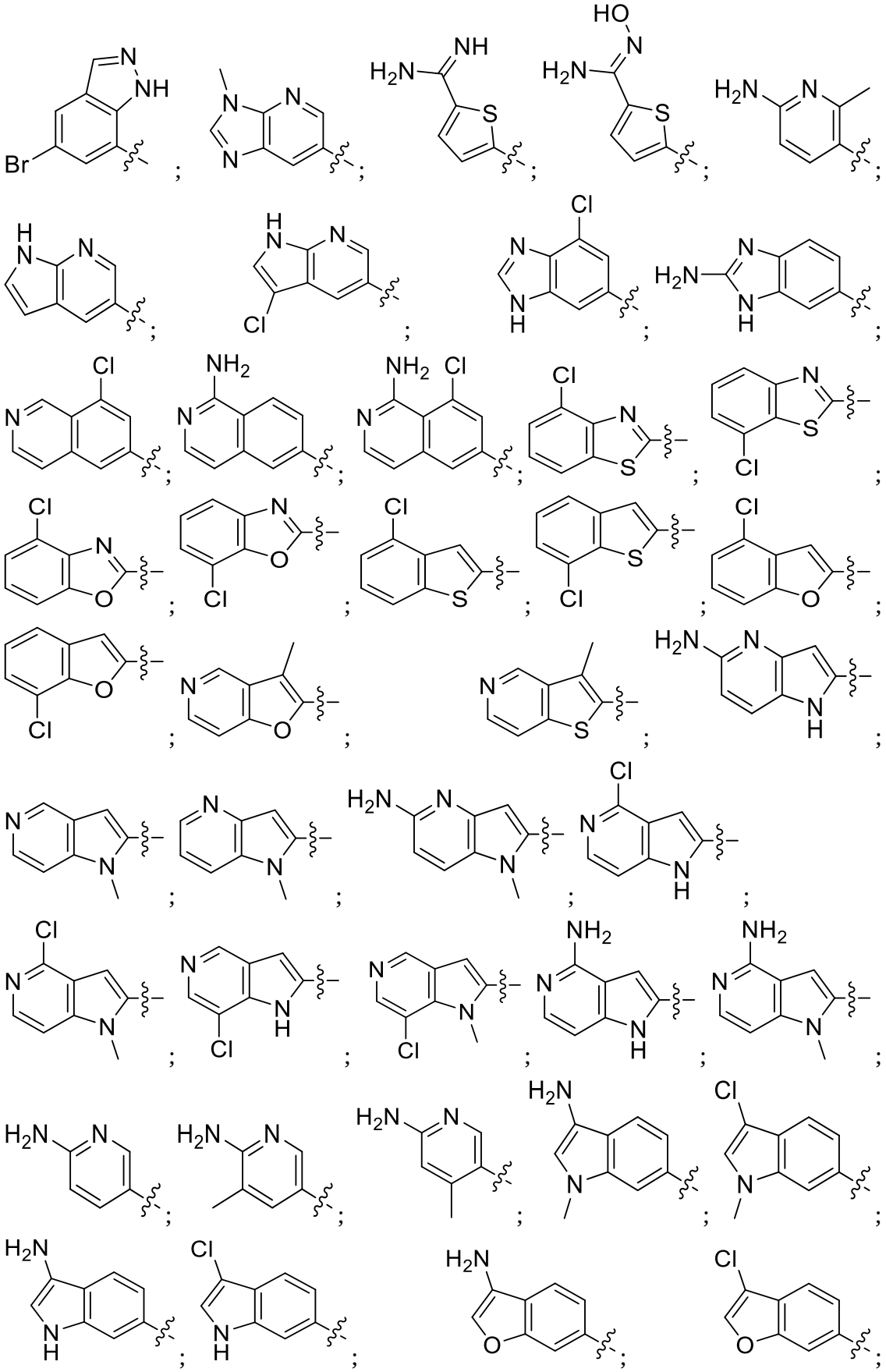
R^1 is a substituted phenyl, or a substituted or unsubstituted heteroaryl,

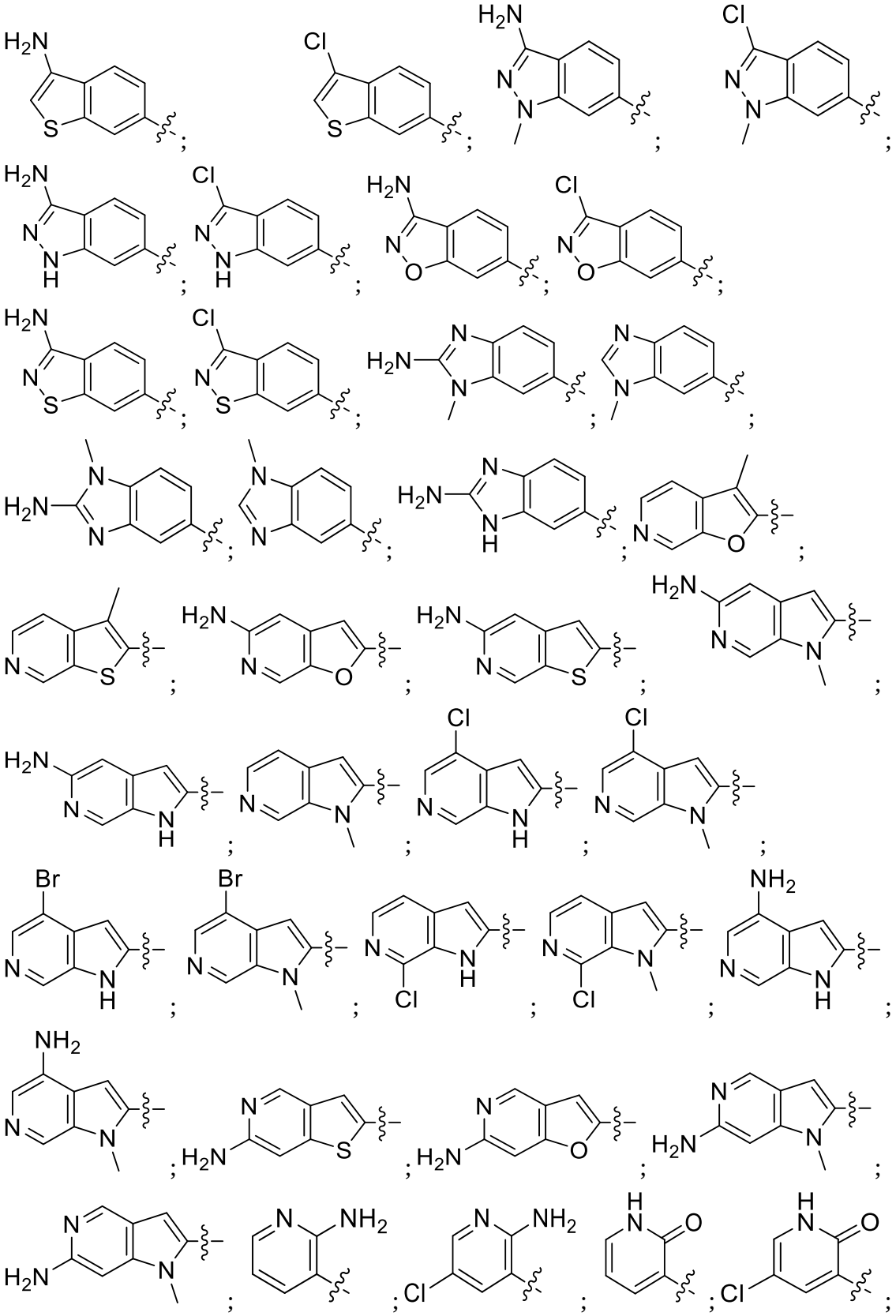
wherein the substituted phenyl of R^1 is phenyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

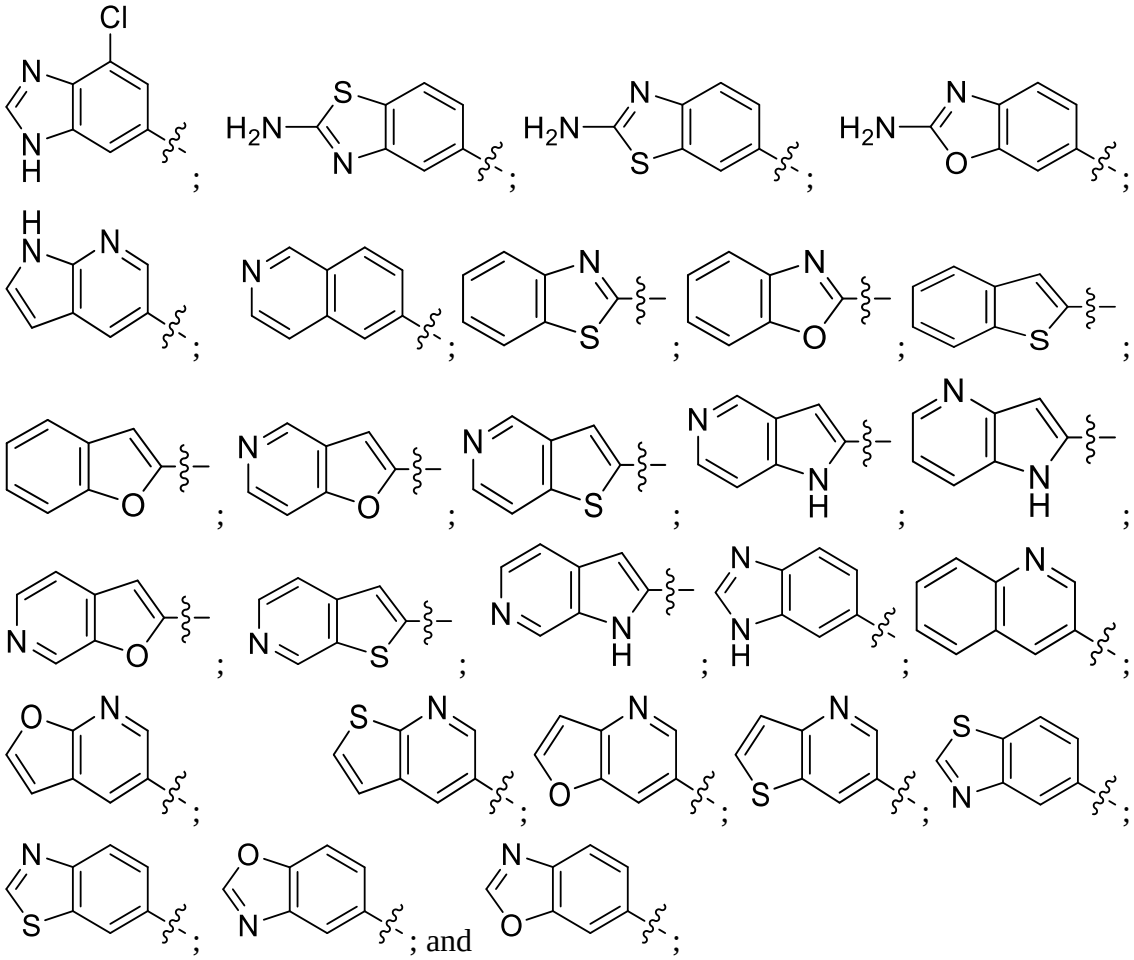
wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl,

wherein the heteroaryl is selected from the group consisting of:









R^2 is alkyl;

R^3 is hydrogen;

or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an unsubstituted or substituted 4-membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

R^{5a} is hydrogen, alkyl, C_3-C_{10} cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, or $C(=O)OR^6$;

R^{5b} is an electron pair or alkyl;

R^6 is hydrogen, alkyl, haloalkyl, or C_{6-10} aryl-C_{1-4} alkyl;

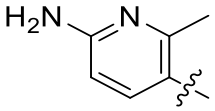
R^8 is alkyl, haloalkyl, aminylalkyl, or substituted or unsubstituted C_{6-10} aryl-C_{1-4} alkyl; and

n is 1, 2, or 3,

provided that

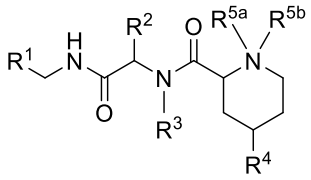
A) R^{5a} is alkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, or $C(=O)OR^6$ or R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$; and

B) when R^{5a} is alkyl or $(CH_2)_nC(=O)OR^6$, R^1 does not have the following structure:



unless R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an unsubstituted or substituted 4-membered heterocyclyl.

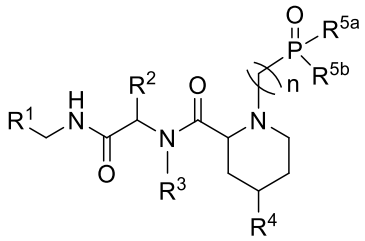
Another example provides a compound having the following Structure (II):



(II)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^{5a}, and R^{5b} are as defined herein.

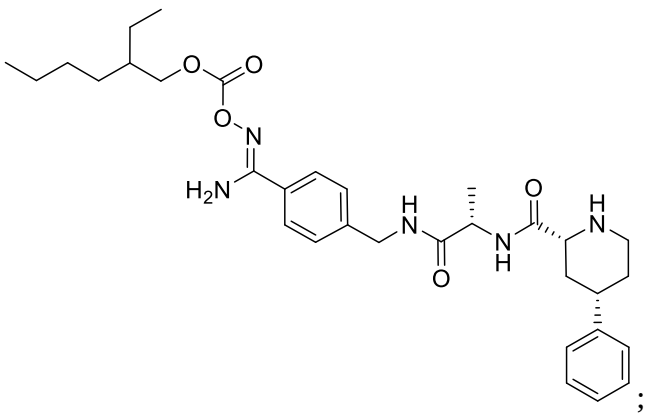
Yet another example provides a compound having the following Structure (III):



(III)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^{5a}, R^{5b} and n are as defined herein.

In one aspect, the present disclosure refers to a compound having one of the structures:



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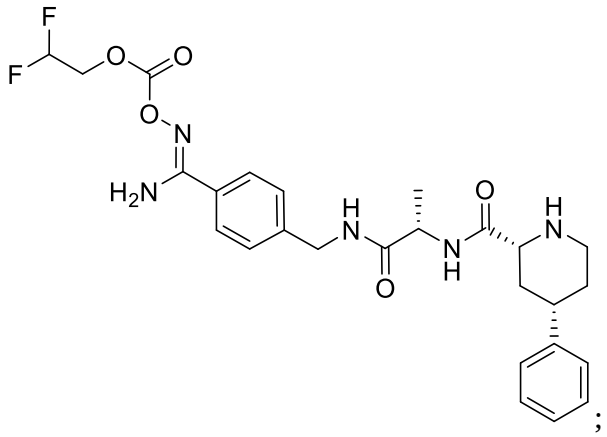
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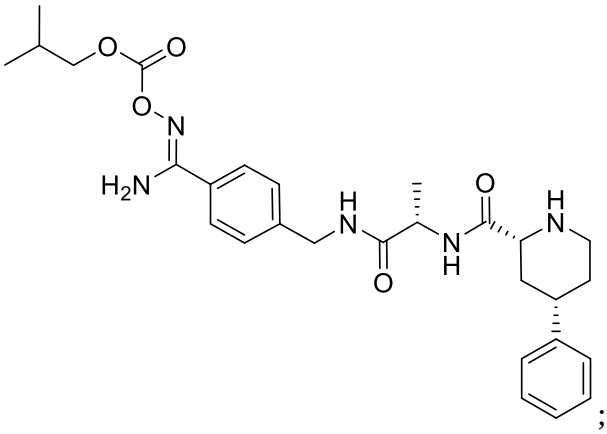
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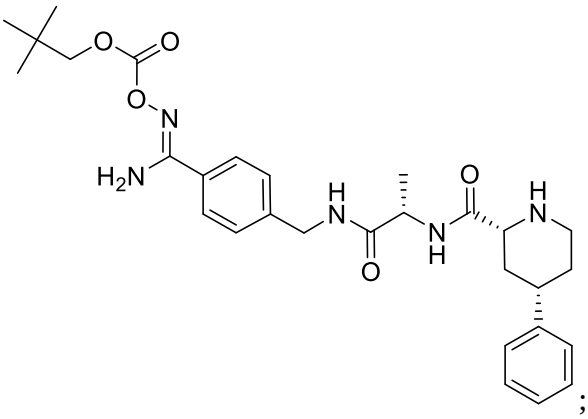
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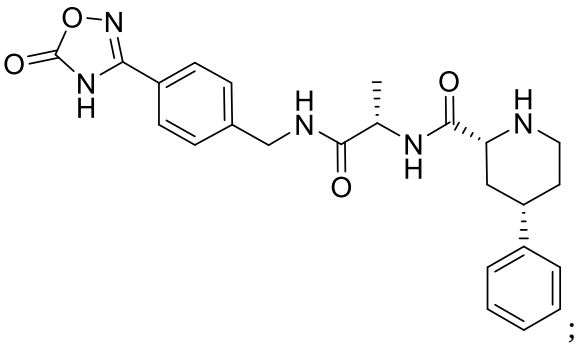
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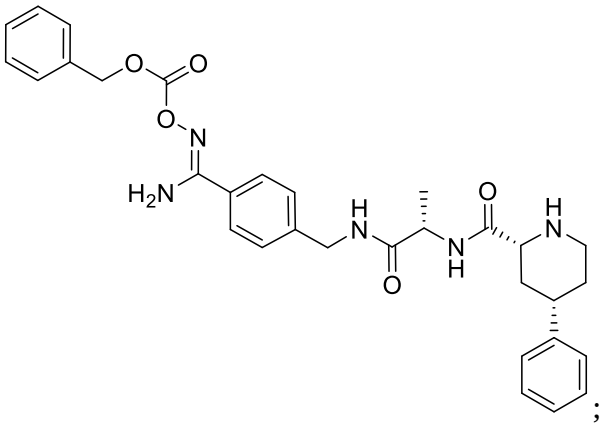
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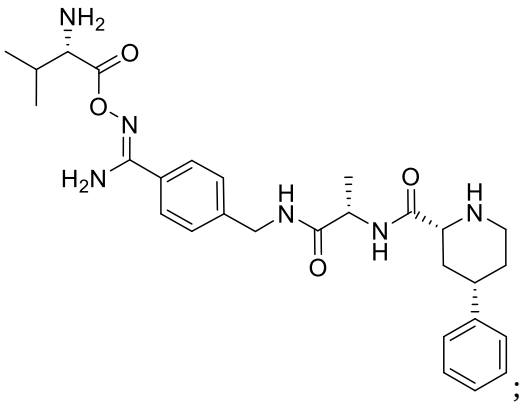
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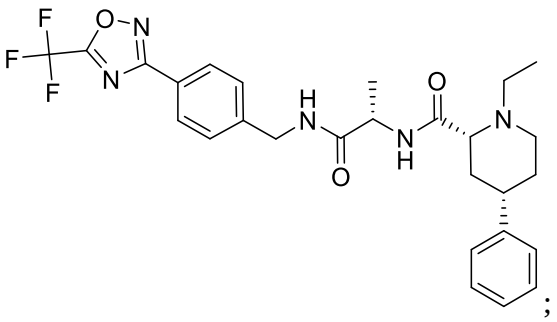
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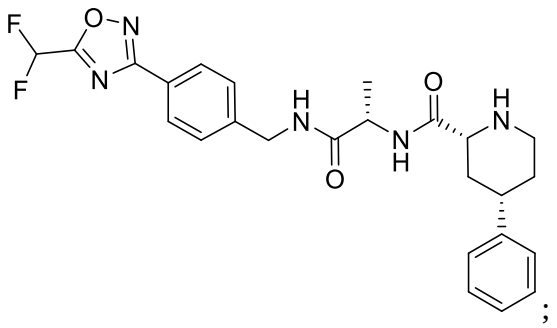
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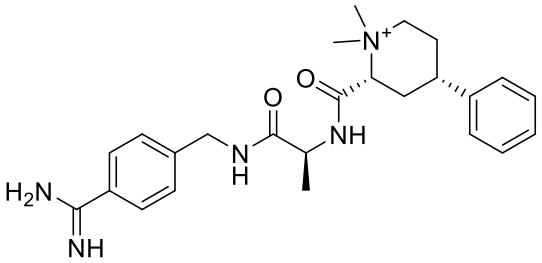

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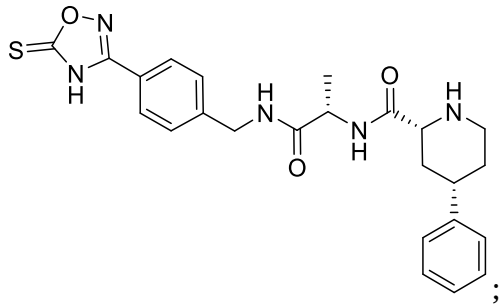

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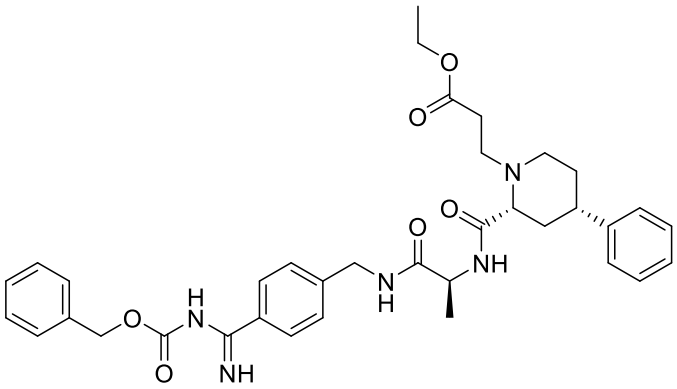

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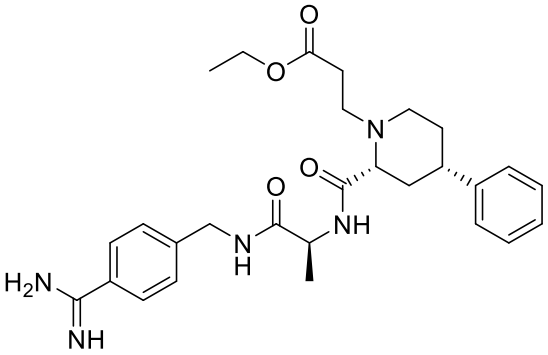

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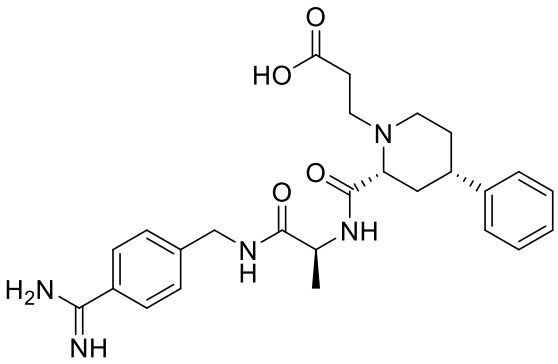
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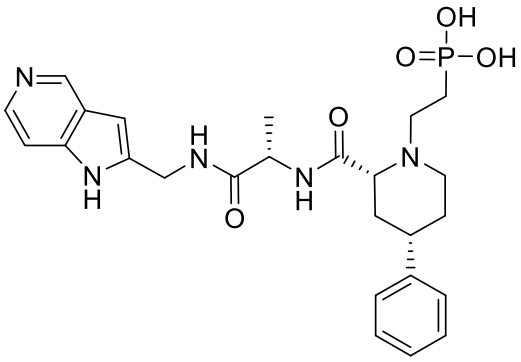
HO
N
O
O
NH
N
H
H2N
NH
;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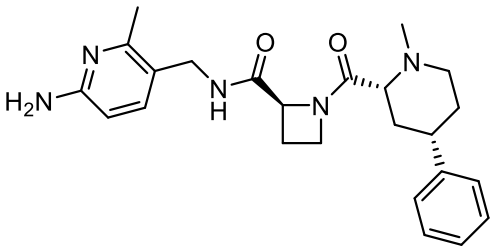
O=P−OH
N
H
N
H
N
O
H
N
O
N
;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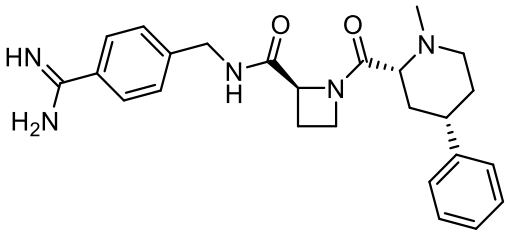
N
H
O
O
N
N
;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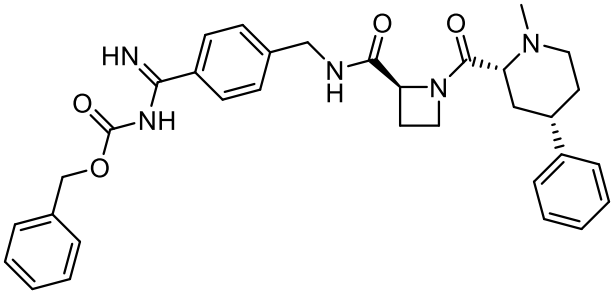
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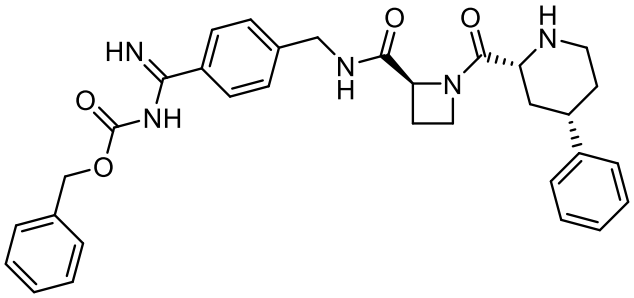

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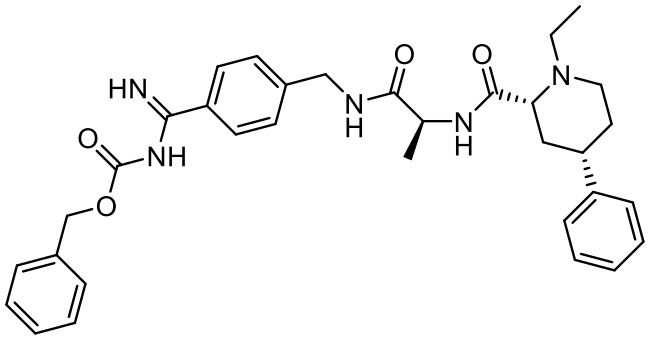

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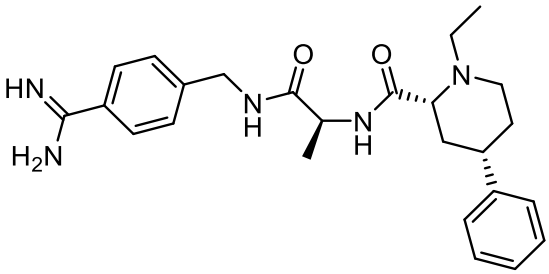

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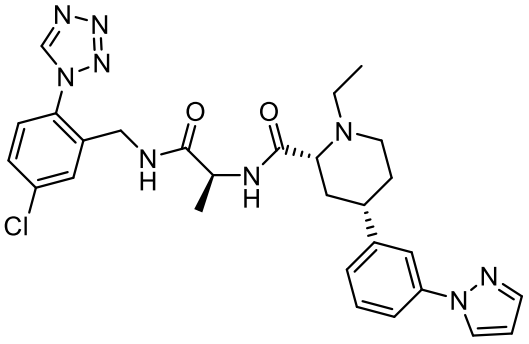

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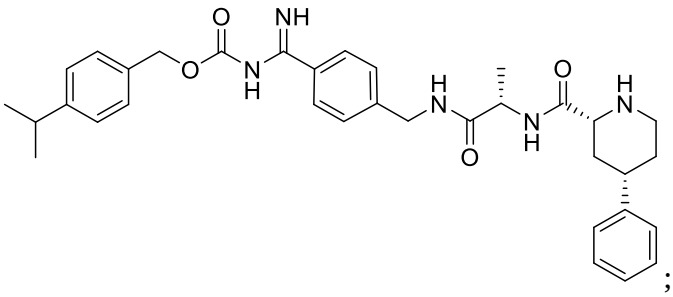

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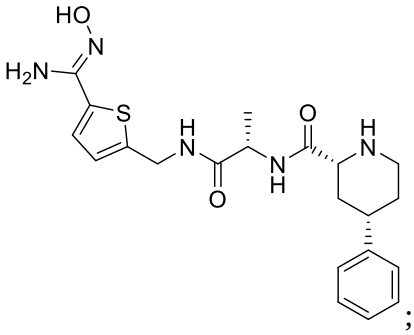
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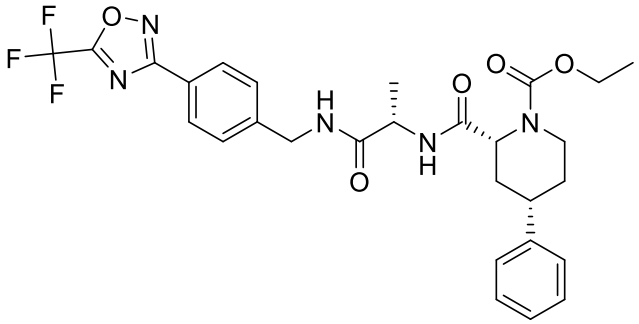
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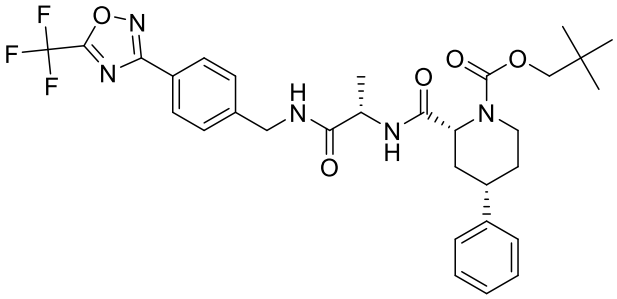
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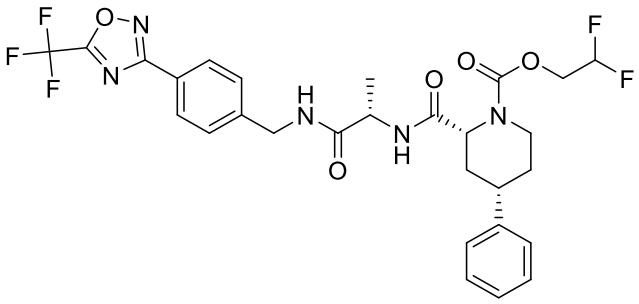
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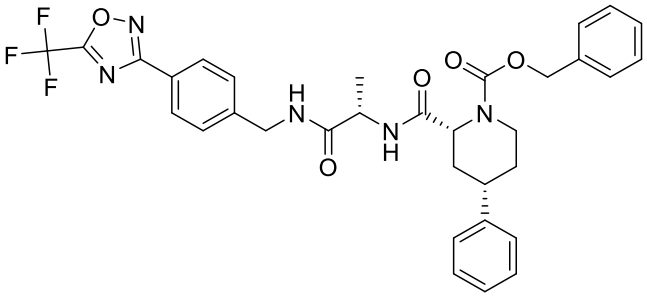
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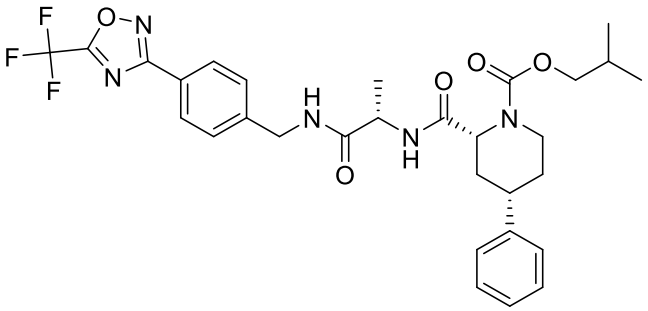
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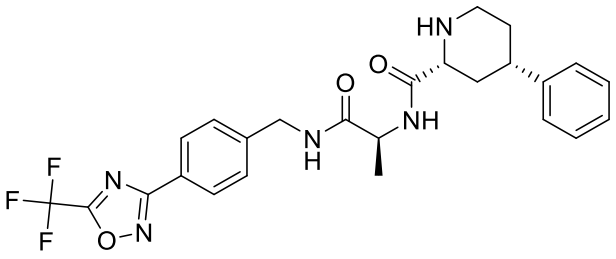
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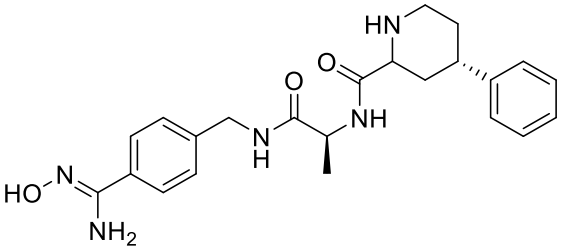
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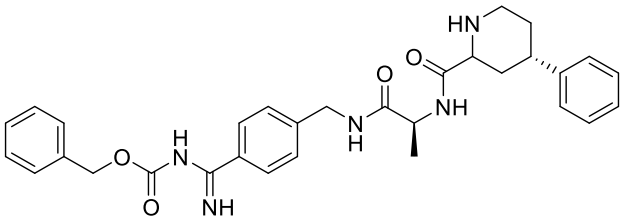
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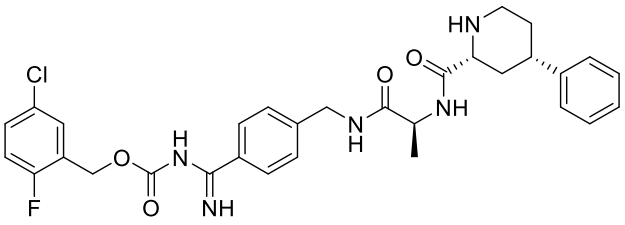
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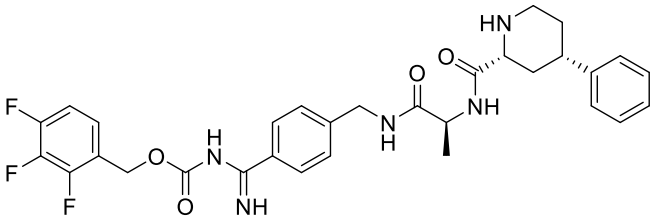
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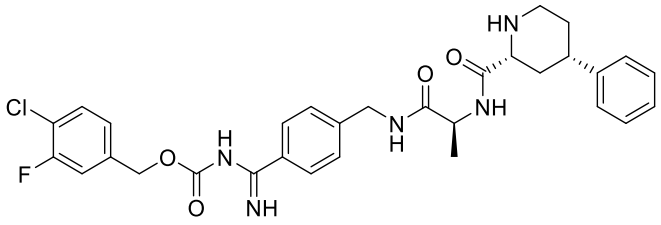

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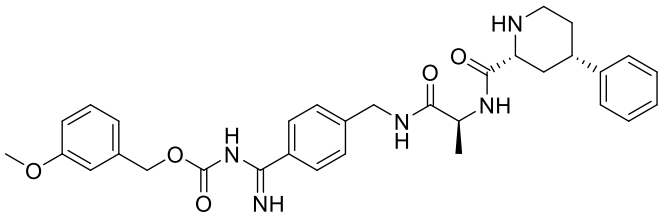

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or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

Additional examples of the present disclosure provide a pharmaceutical composition comprising a compound of Structure (I), Structure (II), or Structure (III), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

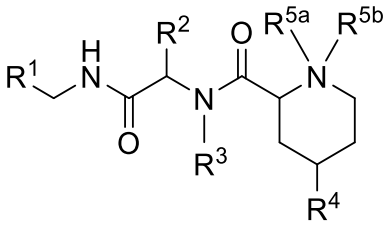
In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds of Structures (I), (II), and (III) are useful in the treatment of MASP-2-associated diseases and disorders, and in the manufacture of medicaments for treating MASP-2-associated diseases and disorders. Accordingly, other examples of the disclosure provide methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Structure (I), Structure (II), or Structure (III), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

These and other examples, and objects will become more apparent when read with the detailed description and figures which follow.

CLAIMS

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



(I)

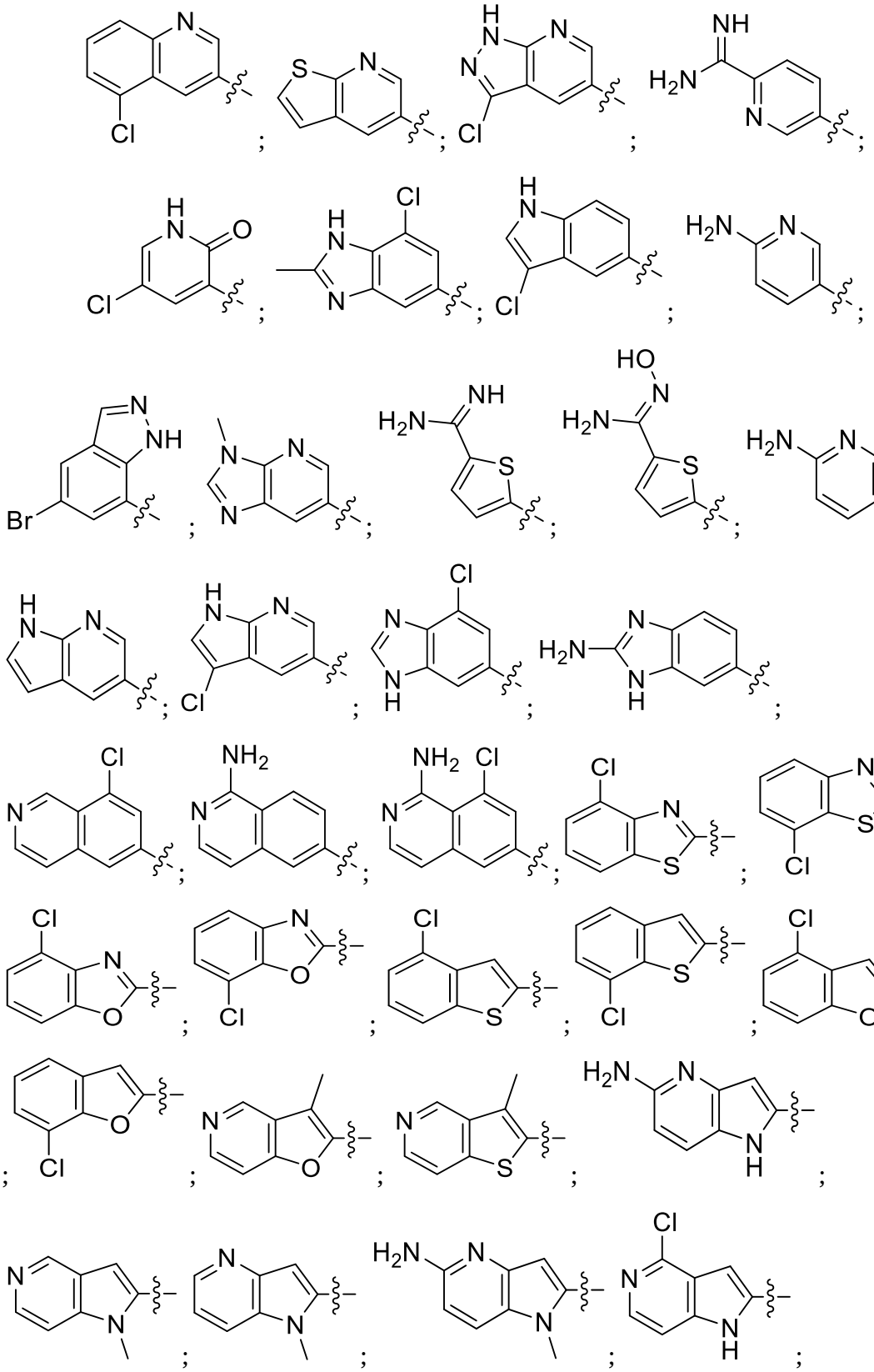
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

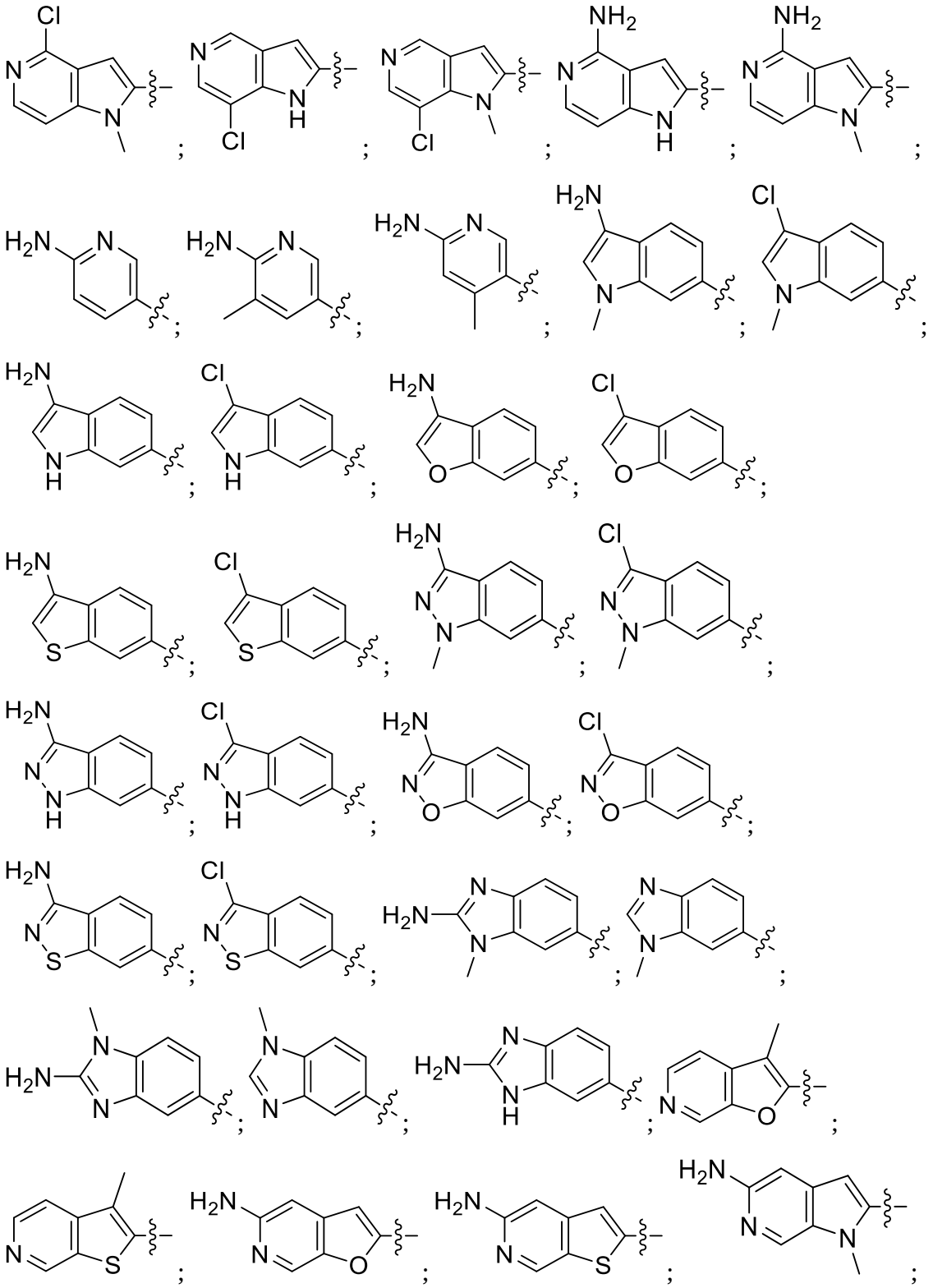
R^1 is a substituted phenyl, or a substituted or unsubstituted heteroaryl,

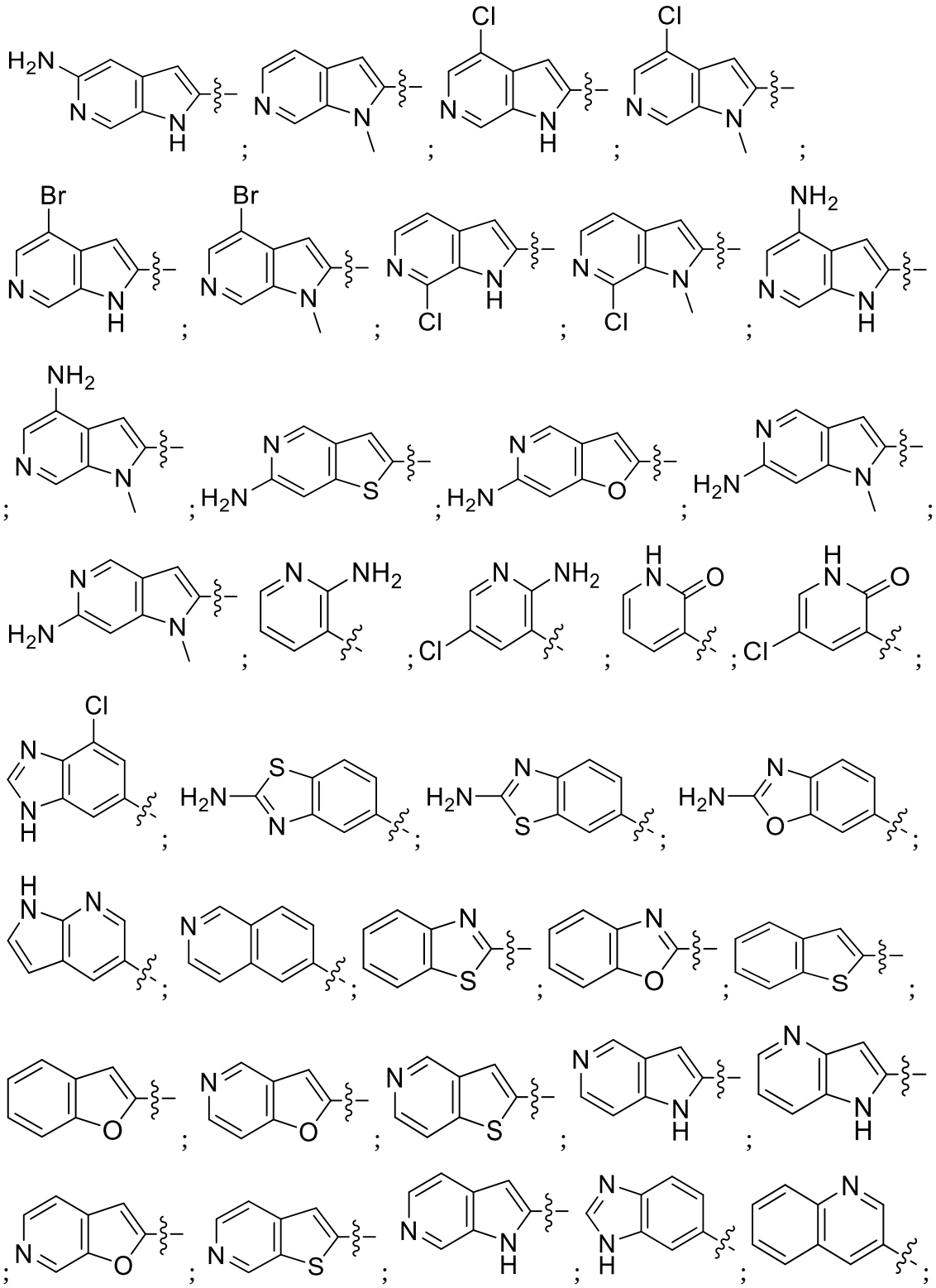
wherein the substituted phenyl of R^1 is phenyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

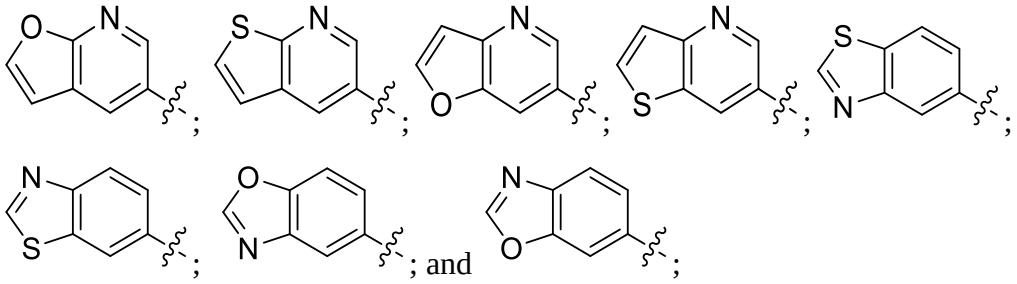
wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl,

wherein the heteroaryl is selected from the group consisting of:









R^2 is alkyl;

R^3 is hydrogen;

or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an unsubstituted or substituted 4-membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

R^{5a} is hydrogen, alkyl, C_3-C_{10} cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, or $C(=O)OR^6$;

R^{5b} is an electron pair or alkyl;

R^6 is hydrogen, alkyl, haloalkyl, or $C_{6\text{-}10}$ aryl-$C_{1\text{-}4}$ alkyl;

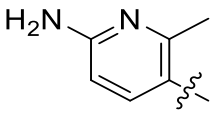
R^8 is alkyl, haloalkyl, aminylalkyl, or substituted or unsubstituted $C_{6\text{-}10}$ aryl-$C_{1\text{-}4}$ alkyl; and

n is 1, 2, or 3,

provided that

A) R^{5a} is alkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, or $C(=O)OR^6$ or R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$; and

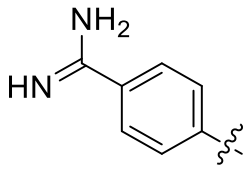
B) when R^{5a} is alkyl or $(CH_2)_nC(=O)OR^6$, R^1 does not have the following structure:



unless R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an unsubstituted or substituted 4-membered heterocyclyl.

2. The compound of claim 1, wherein R^1 is a substituted phenyl.

3. The compound of claim 1, wherein R^1 has one of the following structures:



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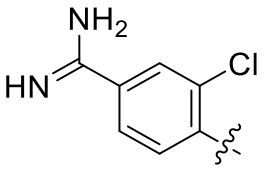

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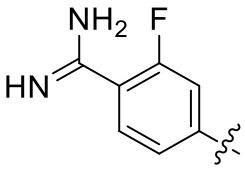

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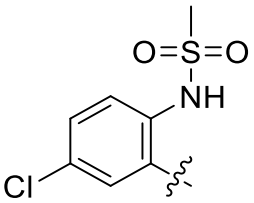

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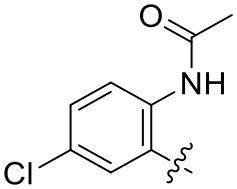

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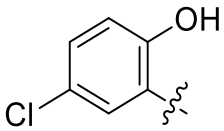

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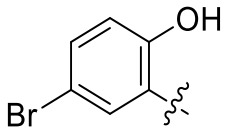

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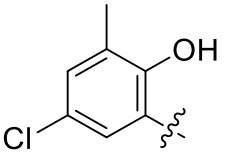

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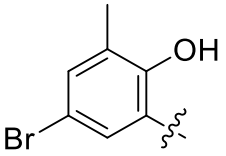

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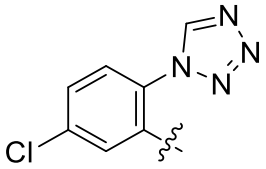

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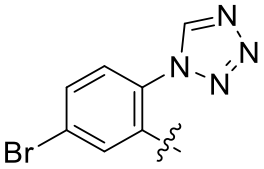

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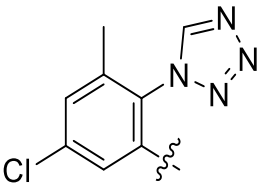

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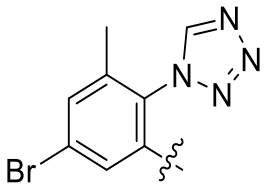


.

4. The compound of claim 1, wherein R^1 is a substituted or unsubstituted heteroaryl.

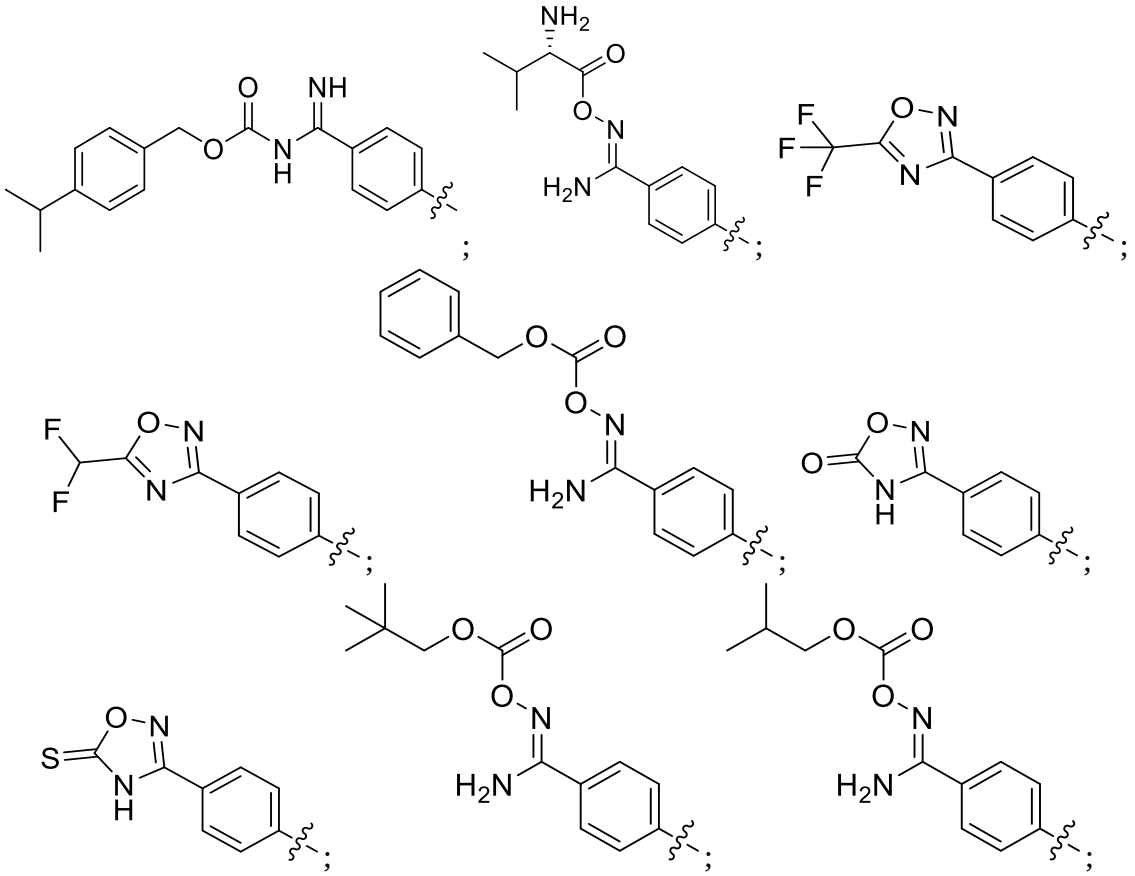
5. The compound of claim 1, wherein R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$.

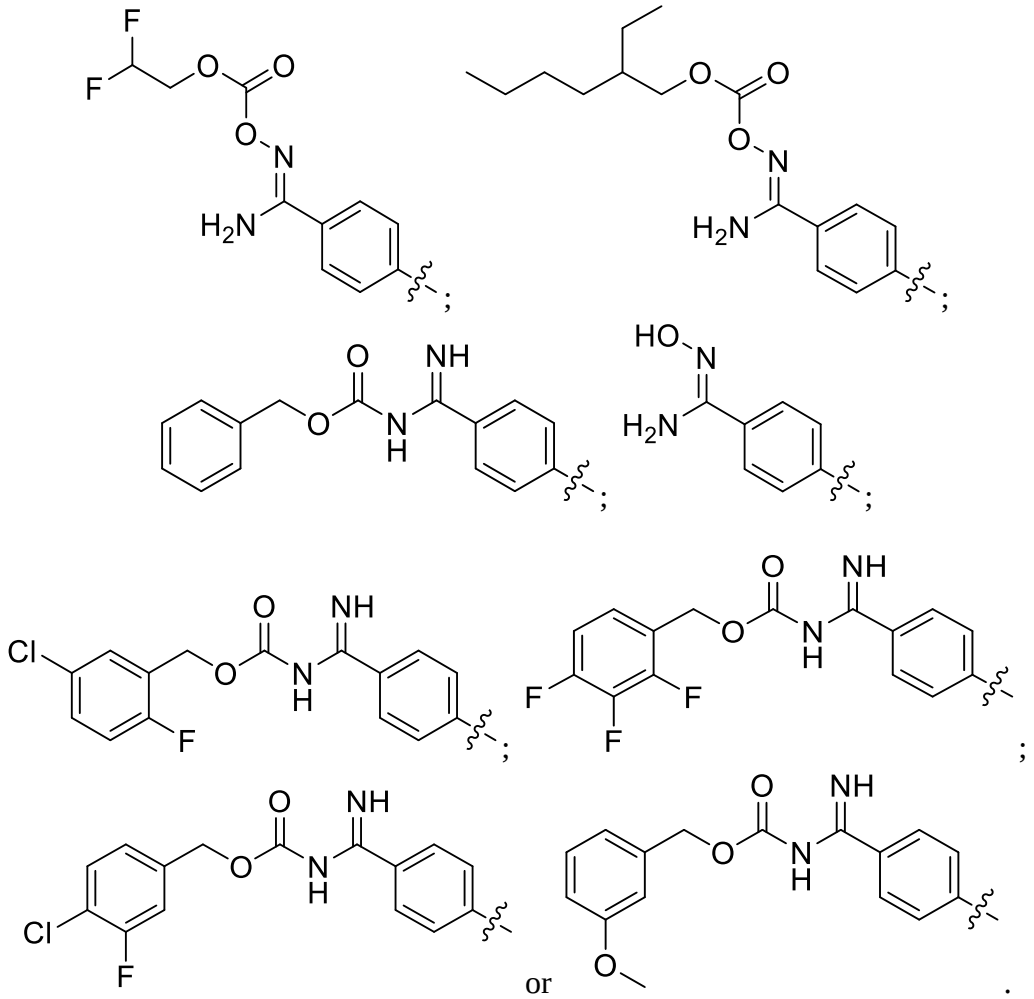
6. The compound of claim 5, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 is a substituted or unsubstituted $C_{6\text{-}10}$ aryl-$C_{1\text{-}4}$ alkyl.

7. The compound of claim 5, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 is an aminylalkyl.

8. The compound of claim 5, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 is an alkyl, a haloalkyl, or a substituted or unsubstituted C_{6-10} aryl-C_{1-4} alkyl.

9. The compound of claim 5, wherein R^1 has one of the following structures:





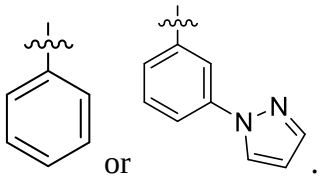
10. The compound of claim 1, wherein R^2 is C_1-C_6 alkyl.

11. The compound of claim 1, wherein R^2 is -CH_3.

12. The compound of claim 1, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an unsubstituted or substituted 4-membered heterocyclyl.

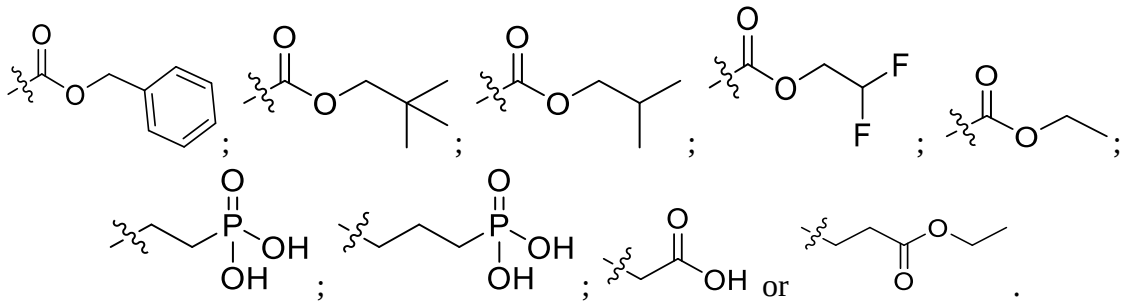
13. The compound of claim 1, wherein R^4 is a substituted or unsubstituted aryl.

14. The compound of claim 1, wherein R^4 has one of the following structures:

 or .

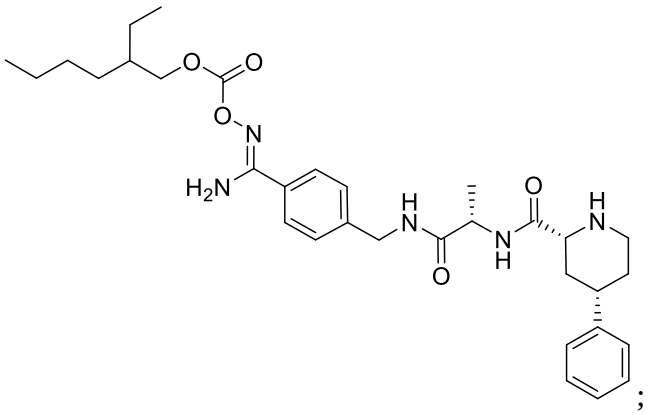
15. The compound of claim 1, wherein R^{5a} is alkyl, $C(=O)OR^6$, phosphonalkyl, or $(CH_2)_nC(=O)OR^6$.

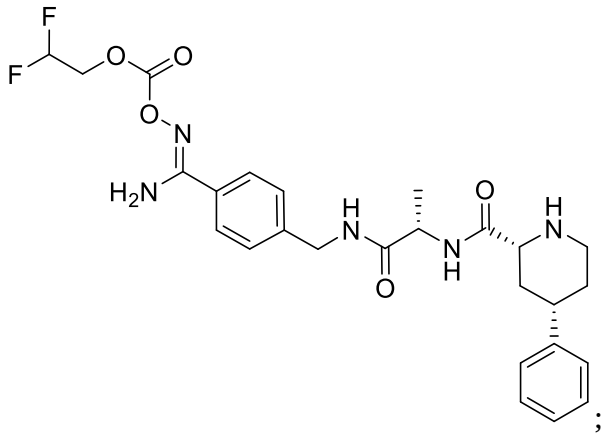
16. The compound of claim 15, wherein R^{5a} has one of the following structures:



17. The compound of claim 1, wherein R^{5b} is an electron pair or alkyl.

18. A compound having one of the structures:

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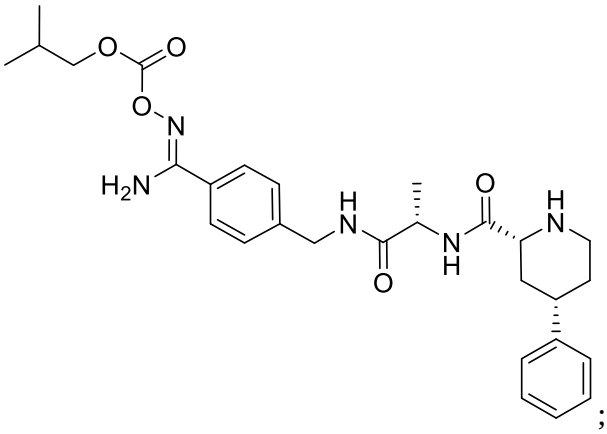
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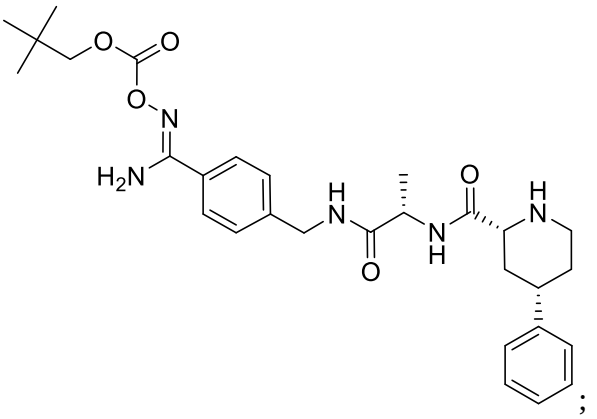
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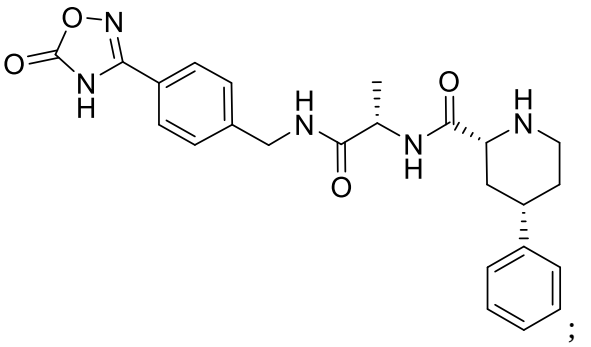
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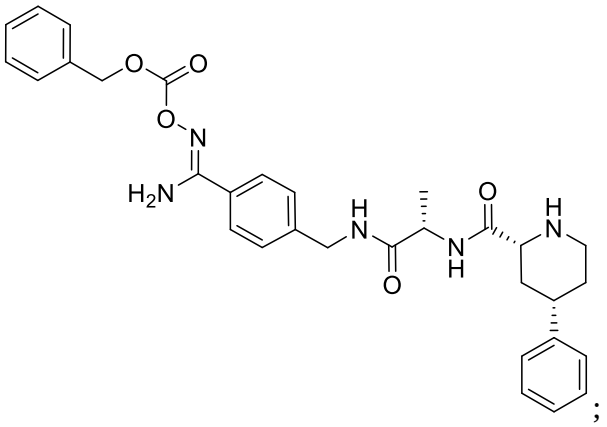
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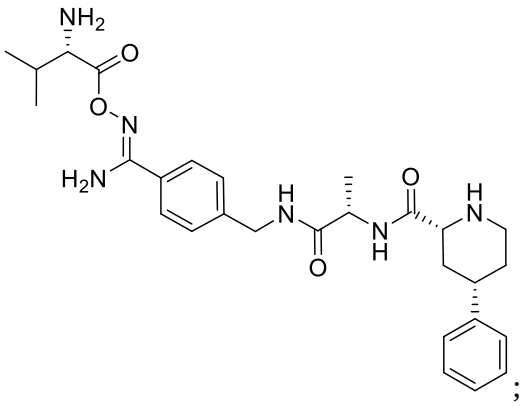
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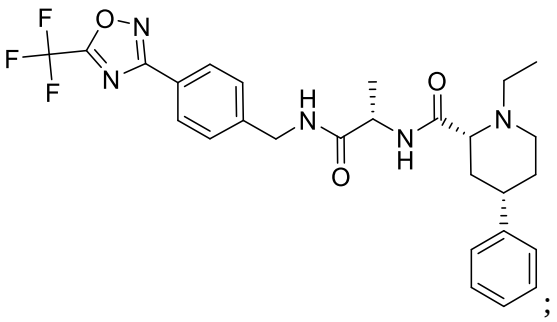
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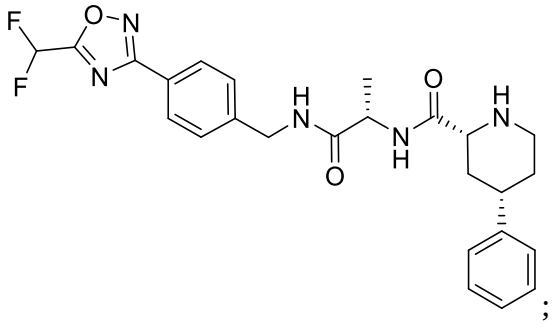
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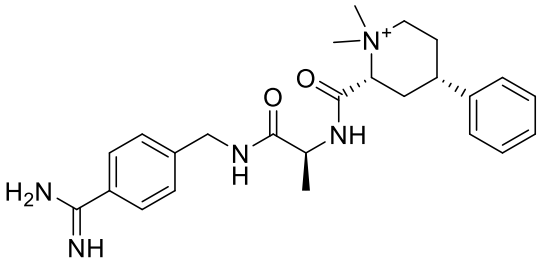

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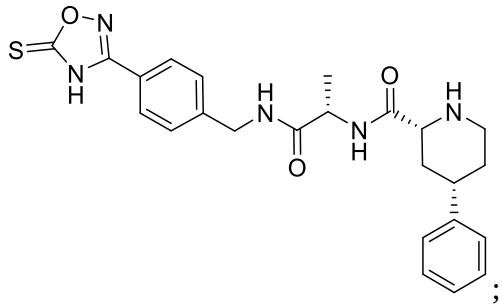

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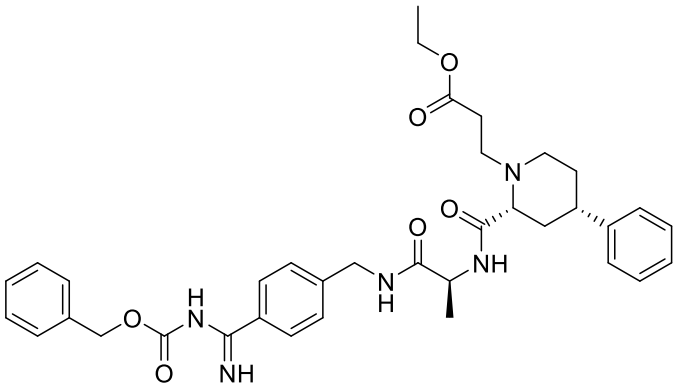

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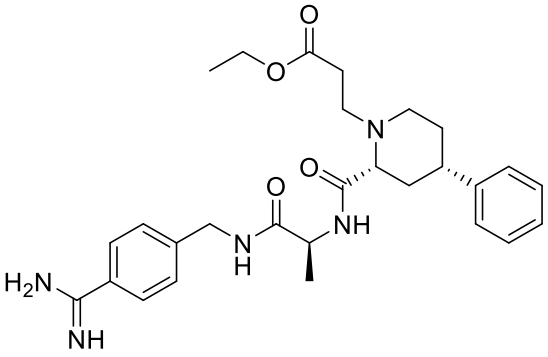

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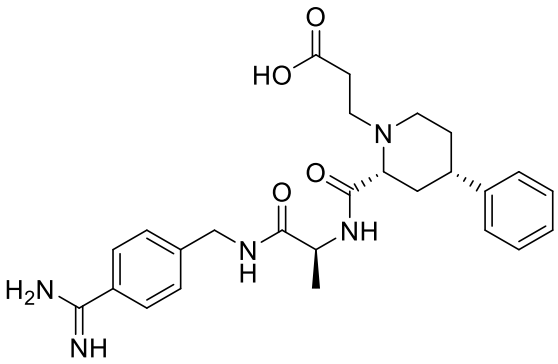
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HO
N
O
O
NH
N
H
H2N
NH
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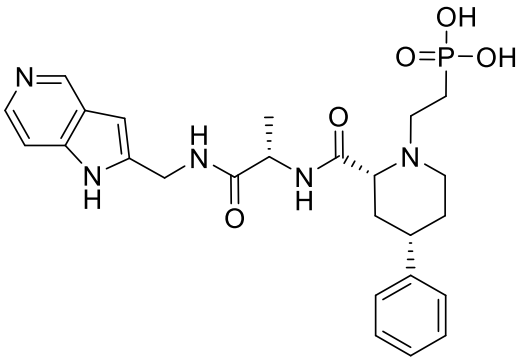
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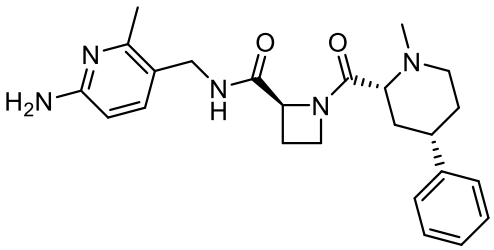
H
N
H
N
O
H
N
O
N
;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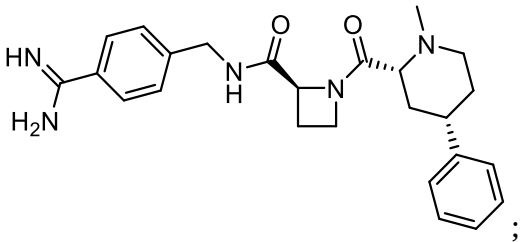
O
N
N
H
N
;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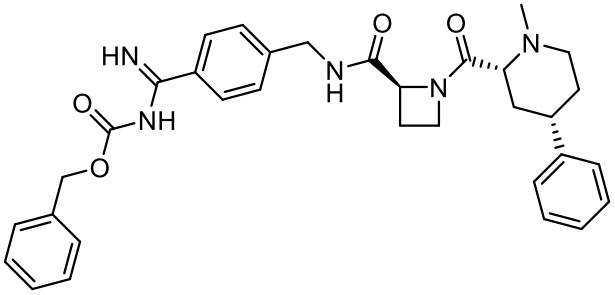
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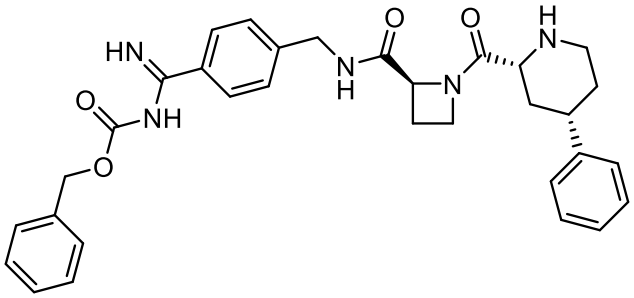

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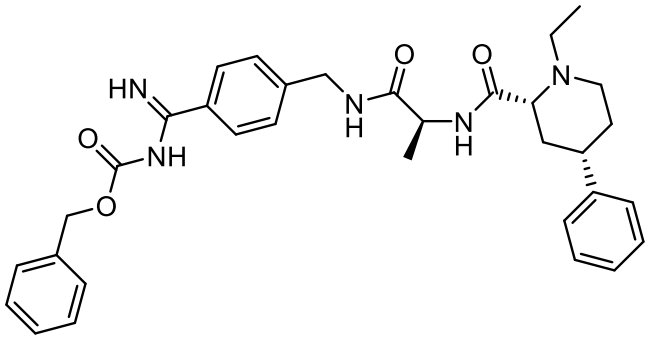

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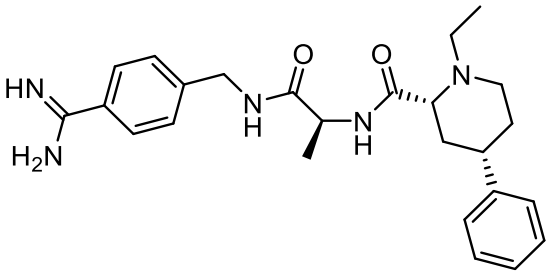

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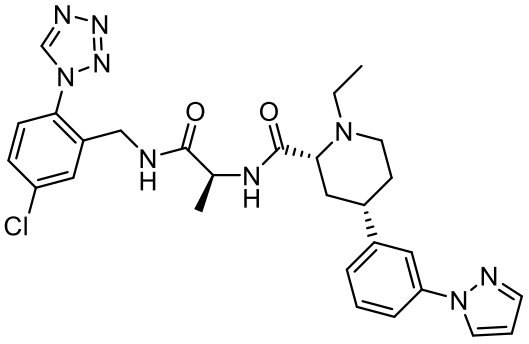

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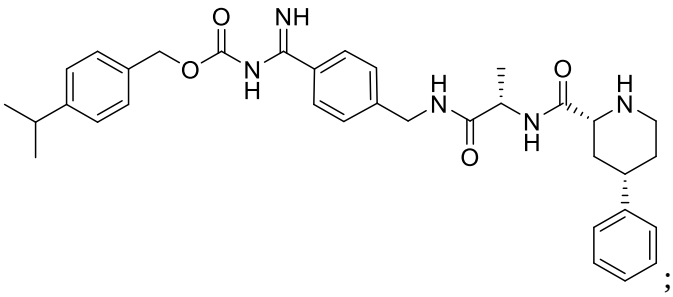

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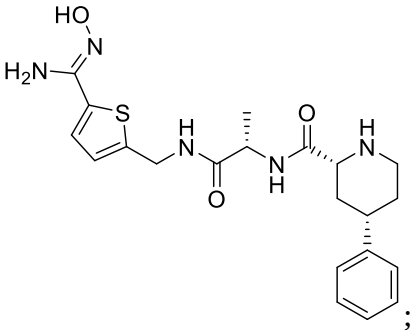
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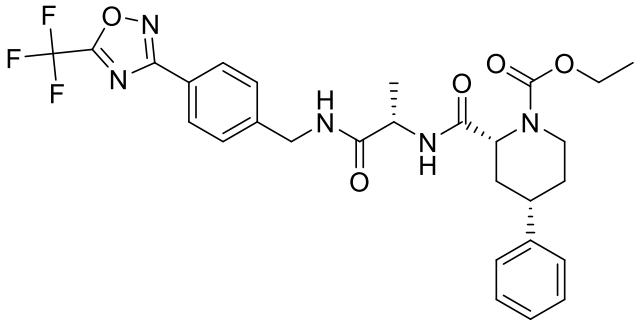
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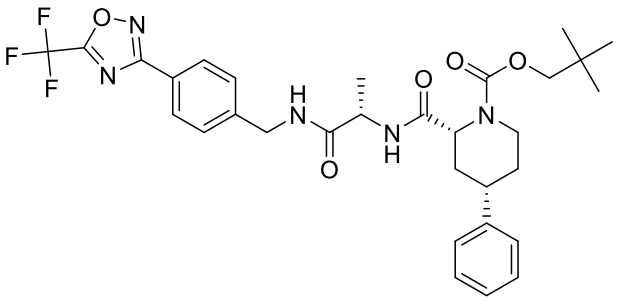
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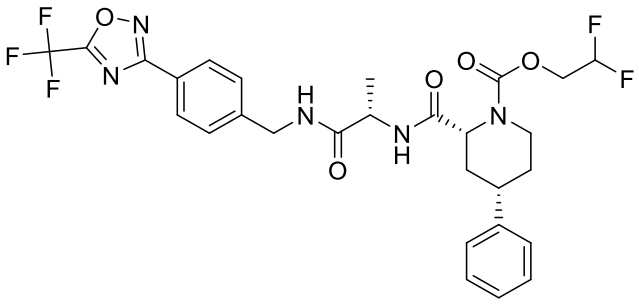
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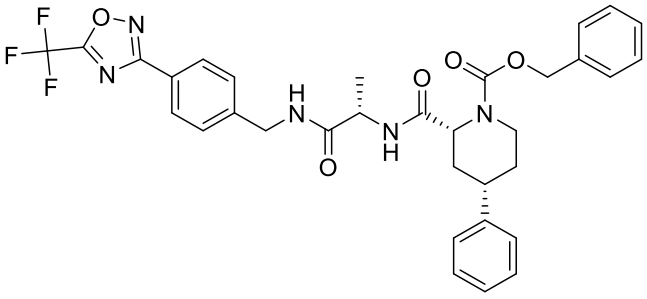
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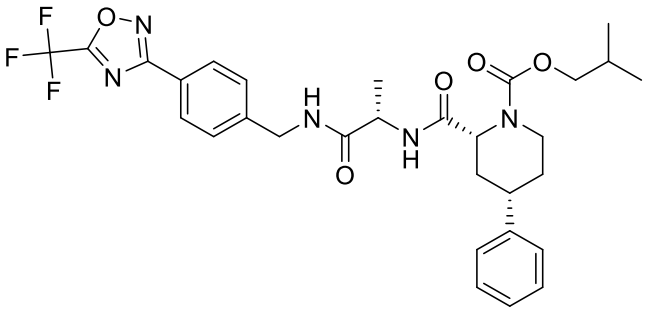
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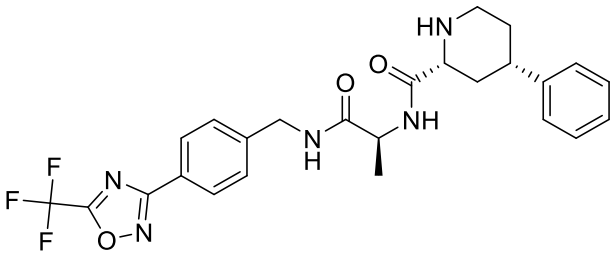
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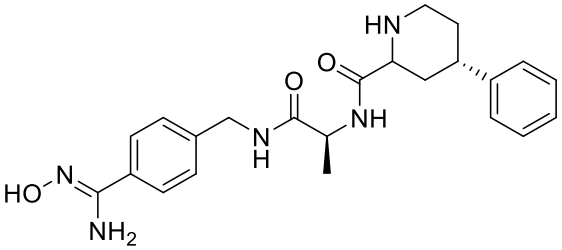
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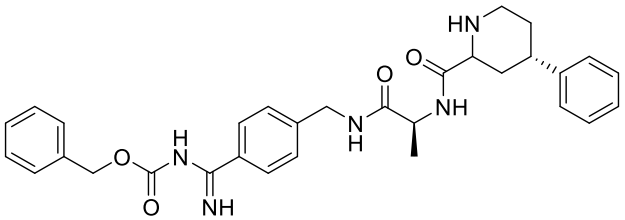
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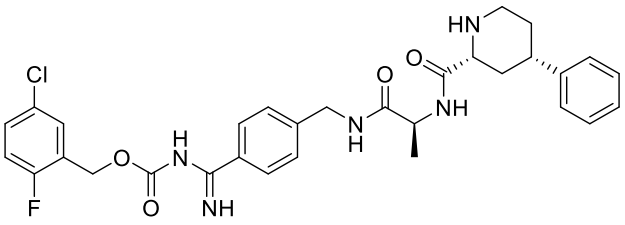
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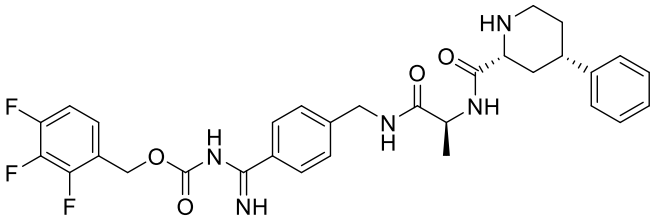
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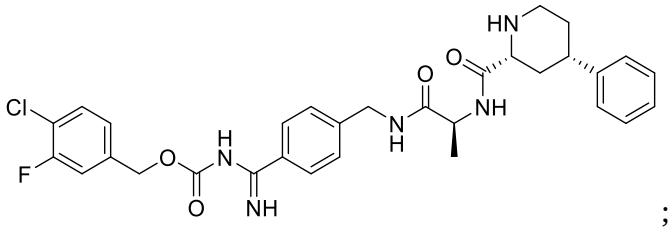

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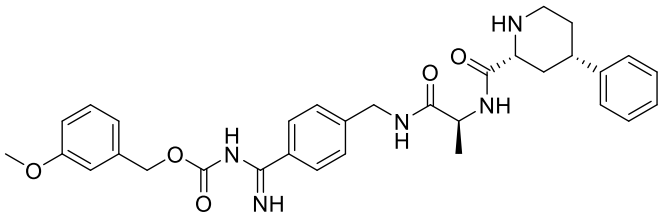

,

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

19. A pharmaceutical composition comprising a compound of claim 1 or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.