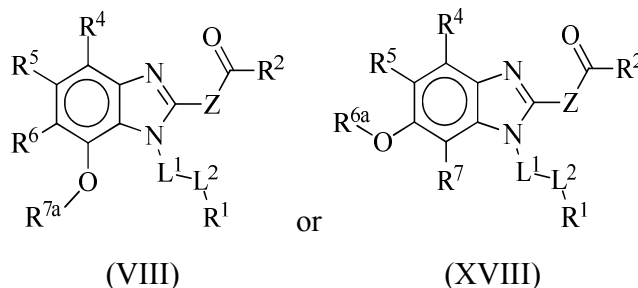
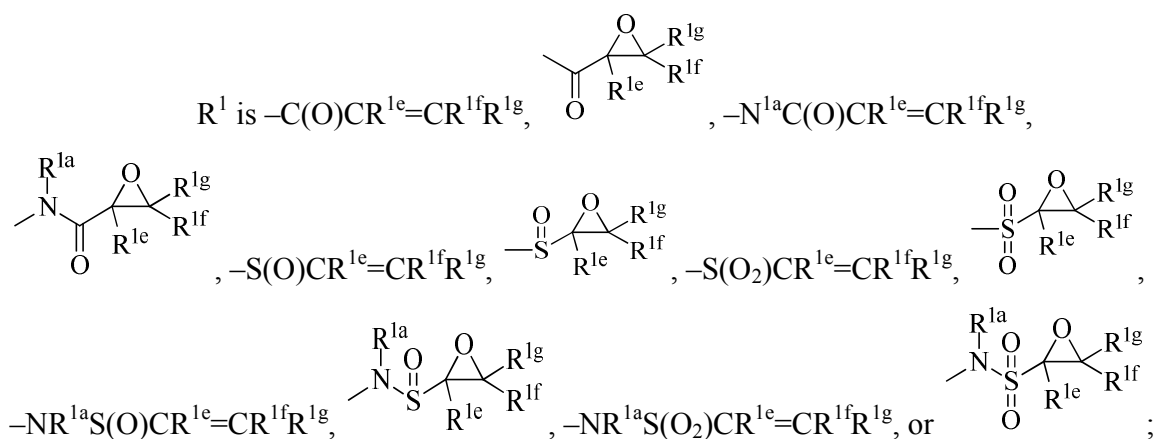


What is claimed is:

1. A compound of Formula VIII or XVIII:



or a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, or solvate thereof;



R^2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

L^1 is a bond, $-O-$, $-S-$, $-N(R^{1A})-$, or $-C(R^{1A}R^{1B})-$, wherein each R^{1A} and R^{1B} is independently hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

L^2 is C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, or heterocyclylene;

Z is NR^{2A} or $CR^{2A}R^{2B}$, wherein each R^{2A} and R^{2B} is independently hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or

heterocyclyl;

each R^4 , R^5 , R^6 , and R^7 is independently (a) hydrogen, cyano, halo, or nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

R^{6a} is (i) C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (ii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

R^{7a} is C_{4-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

each R^{1a} , R^{1b} , R^{1c} , and R^{1d} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or R^{1a} and R^{1c} together with the C and N atoms to which they are attached form heterocyclyl; or R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl; and

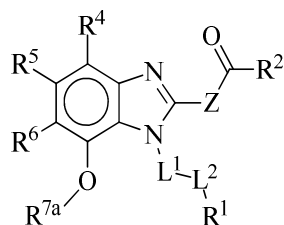
each R^{1e} , R^{1f} , and R^{1g} is independently hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more substituents Q, where each Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with

one or more substituents Q^a ; and (c) $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^bR^c$, $-C(NR^a)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(=NR^a)NR^bR^c$, $-OP(O)(OR^a)_2$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(=NR^d)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$, $-NR^aS(O)_2NR^bR^c$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^bR^c$, and $-S(O)_2NR^bR^c$, wherein each R^a , R^b , R^c , and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q^a ; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more substituents Q^a ;

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^gR^h$, $-C(NR^f)NR^gR^h$, $-OR^f$, $-OC(O)R^f$, $-OC(O)OR^f$, $-OC(O)NR^gR^h$, $-OC(=NR^f)NR^gR^h$, $-OP(O)(OR^f)_2$, $-OS(O)R^f$, $-OS(O)_2R^f$, $-OS(O)NR^gR^h$, $-OS(O)_2NR^gR^h$, $-NR^gR^h$, $-NR^fC(O)R^k$, $-NR^fC(O)OR^k$, $-NR^fC(O)NR^gR^h$, $-NR^fC(=NR^k)NR^gR^h$, $-NR^fS(O)R^k$, $-NR^fS(O)_2R^k$, $-NR^fS(O)NR^gR^h$, $-NR^fS(O)_2NR^gR^h$, $-SR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-S(O)NR^gR^h$, and $-S(O)_2NR^gR^h$; wherein each R^f , R^g , R^h , and R^k is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^g and R^h together with the N atom to which they are attached form heterocyclyl.

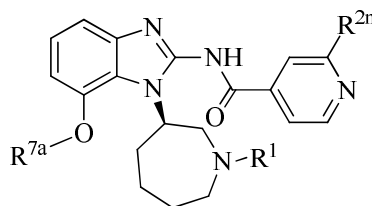
2. The compound of claim 1, having the structure of Formula VIII:



(VIII)

or a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, or solvate thereof.

3. The compound of claim 2, having the structure of Formula XIa:



(XIa)

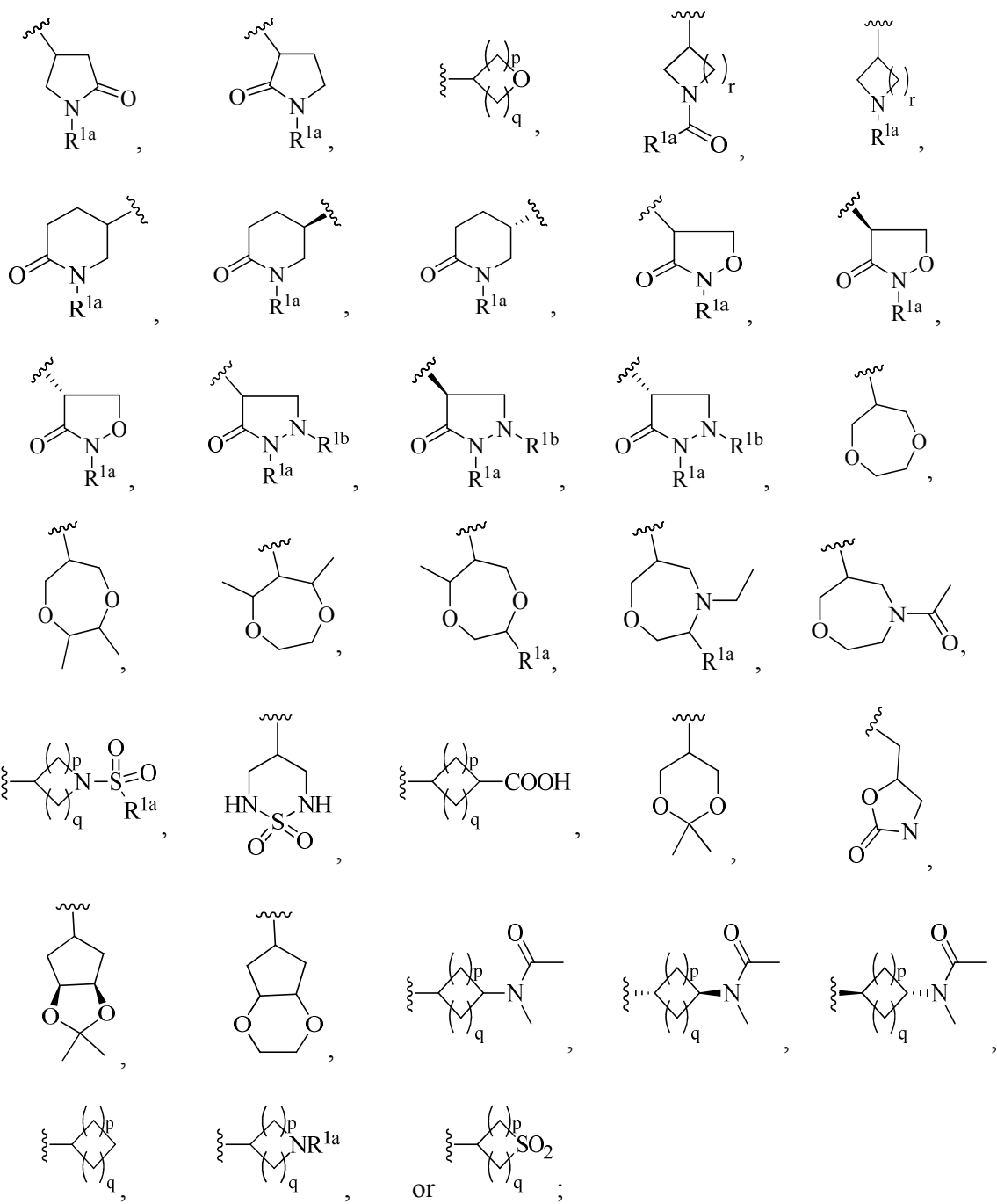
or a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, or solvate thereof; wherein R^{2n} is C_{1-6} alkyl optionally substituted with one or more substituents Q or $-OR^{1a}$.

4. The compound of claim 3, wherein R^{2n} is methyl, monofluoromethyl, difluoromethyl, trifluoromethyl, $-OH$, or $-OCH_3$.

5. The compound of any one of claims 1 to 4, wherein R^{7a} is C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q.

6. The compound of claim 5, wherein R^{7a} is heterocyclyl, optionally substituted with one or more substituents Q.

7. The compound of claim 5, wherein R^{7a} is

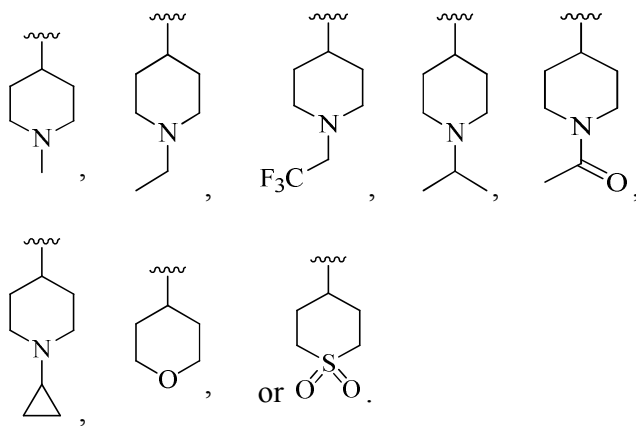


wherein:

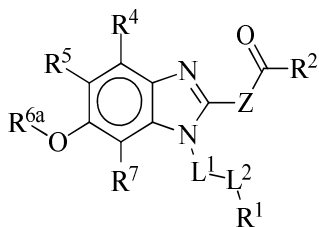
p and q are each independently an integer of 0, 1, or 3, with the proviso that the total of p and q is no less than 1; and

each r is independently an integer of 0, 1, 2, 3, 4, 5, or 6.

8. The compound of claim 5, wherein R^{7a} is



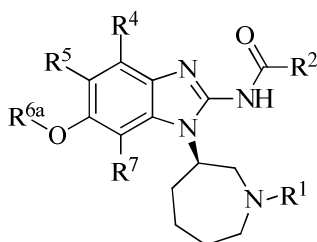
9. The compound of claim 1, having the structure of Formula XVIII:



(XVIII)

or a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, or solvate thereof.

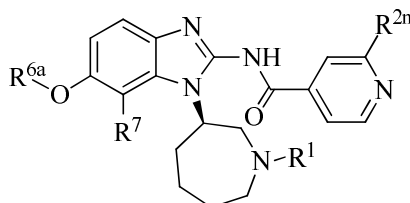
10. The compound of claim 9, having the structure of Formula XIX:



(XIX)

or a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, or solvate thereof.

11. The compound of claim 10, having the structure of Formula XXa:



(XXa)

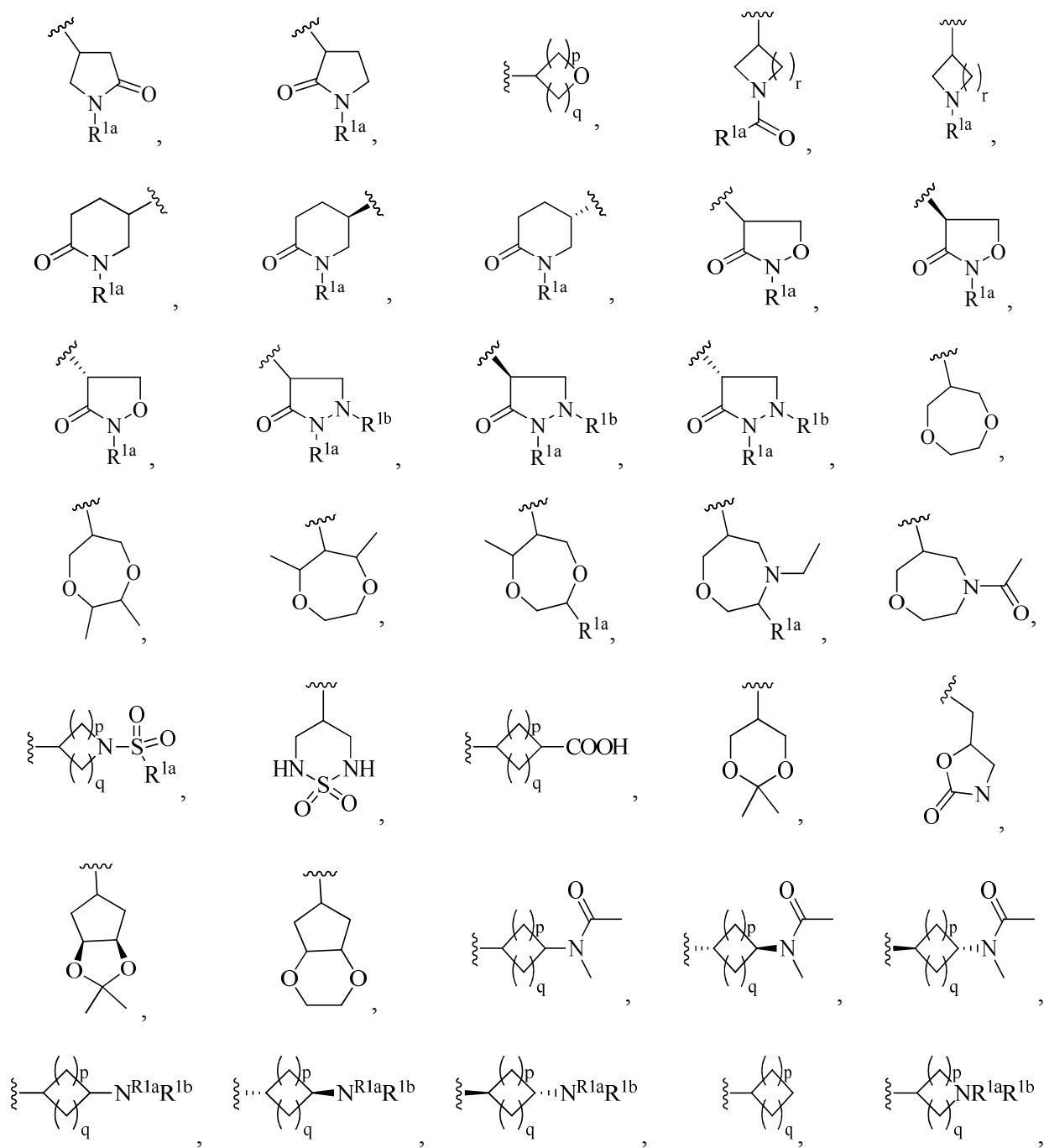
or a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, or solvate thereof; wherein R²ⁿ is C₁₋₆ alkyl optionally substituted with one or more substituents Q or -OR^{1a}.

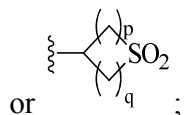
12. The compound of claim 11, wherein R²ⁿ is methyl, monfluoromethyl, difluoromethyl, trifluoromethyl, -OH, or -OCH₃.

13. The compound of any one of claims 1 and 9 to 12, wherein R⁷ is chloro, methyl, monofluoromethyl, difluoromethyl, trifluoromethyl, or -OR^{1a}.

14. The compound of claim 13, wherein R⁷ is chloro.

15. The compound of any one of claims 1 and 9 to 14, wherein R^{6a} is:



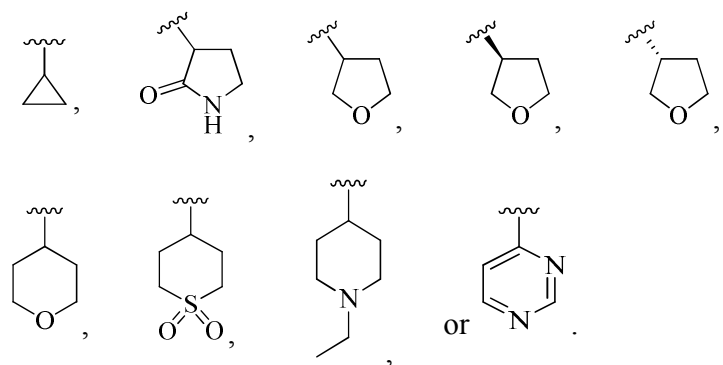


wherein:

p and q are each independently an integer of 0, 1, or 3, with the proviso that the total of p and q is no less than 1; and

each r is independently an integer of 0, 1, 2, 3, 4, 5, or 6.

16. The compound of any one of claims 1 and 9 to 15, wherein R^{6a} is:



17. The compound of any one of claims 1 to 16, wherein L¹ is a bond, -O-, -N(R^{1A})-, or -C(R^{1A}R^{1B})-.

18. The compound of claim 17, wherein L¹ is a bond.

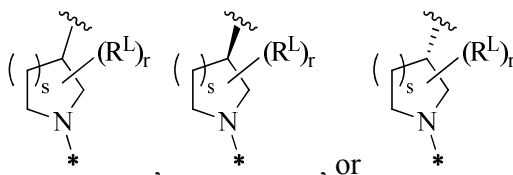
19. The compound of claim 17, wherein L¹ is -O-.

20. The compound of claim 17, wherein L¹ is -NH- or -CH₂-.

21. The compound of any one of claims 1 to 20, wherein L² is C₃₋₁₀ cycloalkylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more substituents Q.

22. The compound of claim 21, wherein L^2 is heteroarylene or heterocyclylene, each of which is optionally substituted with one or more substituents Q.

23. The compound of claim 21, wherein L^2 is:



wherein:

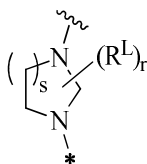
r is an integer of 0, 1, 2, 3, 4, 5, or 6;

s is an integer of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

each R^L is independently (i) hydrogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; or

two R^L together, when there are two or more R^L attached to the same ring, are linked together to form (i) a bond, $-O-$, $-NR^N-$, or $-S-$; or (ii) C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, or C_{2-6} heteroalkenylene, each of which is optionally substituted with one or more substituents Q.

24. The compound of claim 21, wherein L^2 is:



wherein:

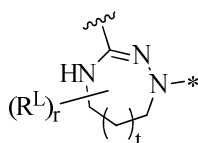
r is an integer of 0, 1, 2, 3, 4, 5, or 6;

s is an integer of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

each R^L is independently (i) hydrogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; or

two R^L together, when there are two or more R^L attached to the same ring, are linked together to form (i) a bond, $-O-$, $-NR^N-$, or $-S-$; or (ii) C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, or C_{2-6} heteroalkenylene, each of which is optionally substituted with one or more substituents Q.

25. The compound of claim 21, wherein L^2 is:



wherein:

r is an integer of 0, 1, 2, 3, 4, 5, or 6;

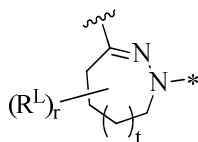
t is an integer of 0, 1, 2, 3, 4, 5, or 6; and

each R^L is independently (i) hydrogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$,

$-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(=\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$,
 $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or
 $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$; or

two R^L together, when there are two or more R^L attached to the same ring, are linked together to form (i) a bond, $-\text{O}-$, $-\text{NR}^N-$, or $-\text{S}-$; or (ii) C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, or C_{2-6} heteroalkenylene, each of which is optionally substituted with one or more substituents Q.

26. The compound of claim 21, wherein L^2 is:



wherein:

r is an integer of 0, 1, 2, 3, 4, 5, or 6;

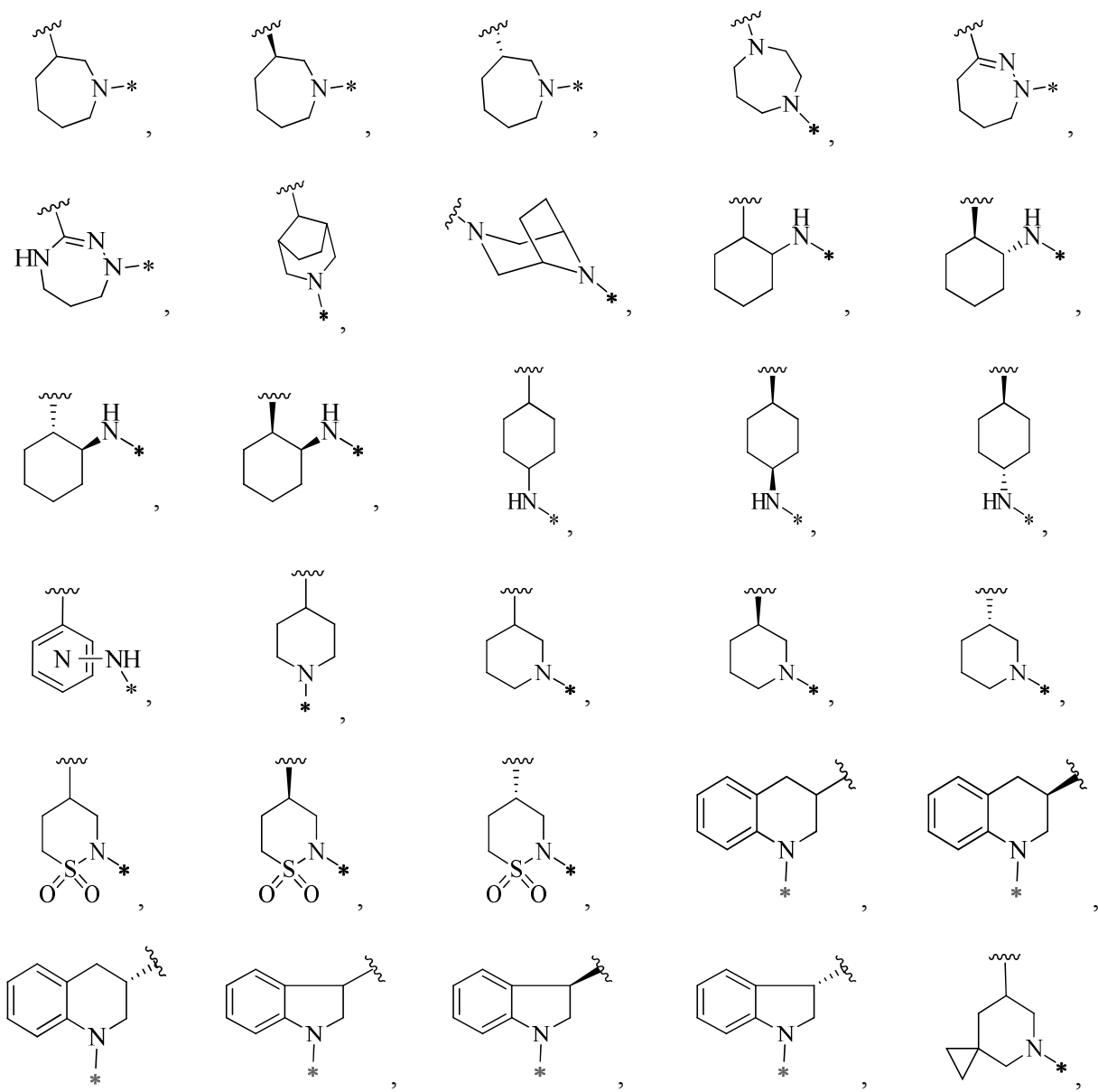
t is an integer of 0, 1, 2, 3, 4, 5, or 6; and

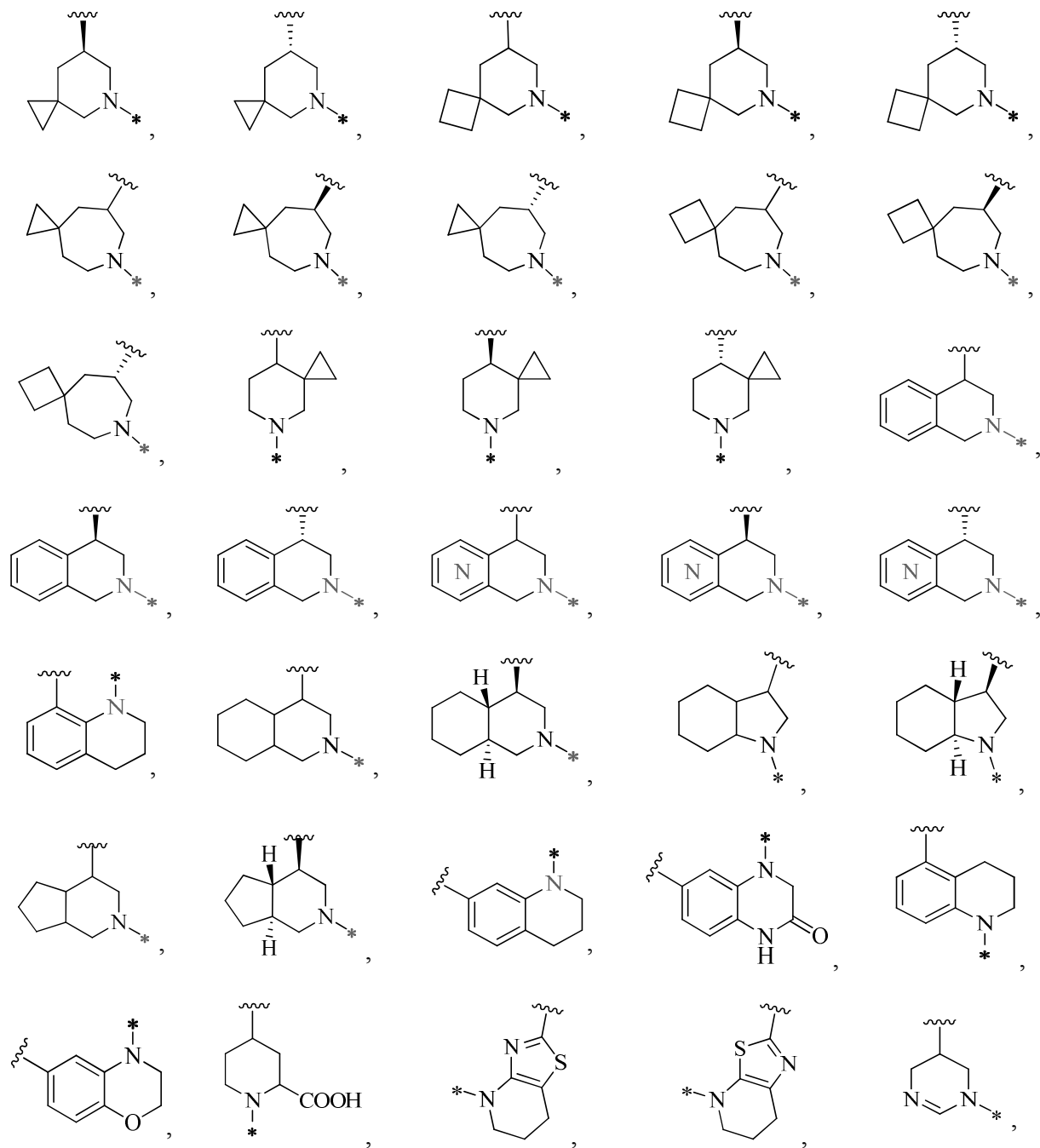
each R^L is independently (i) hydrogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or (iii) $-\text{C}(\text{O})\text{R}^{1a}$, $-\text{C}(\text{O})\text{OR}^{1a}$, $-\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{C}(\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{R}^{1a}$, $-\text{OC}(\text{O})\text{OR}^{1a}$, $-\text{OC}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OC}(=\text{NR}^{1a})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})\text{R}^{1a}$, $-\text{OS}(\text{O})_2\text{R}^{1a}$, $-\text{OS}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{OS}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{OR}^{1d}$, $-\text{NR}^{1a}\text{C}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{C}(=\text{NR}^{1d})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{R}^{1d}$, $-\text{NR}^{1a}\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, $-\text{NR}^{1a}\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$, $-\text{SR}^{1a}$, $-\text{S}(\text{O})\text{R}^{1a}$, $-\text{S}(\text{O})_2\text{R}^{1a}$, $-\text{S}(\text{O})\text{NR}^{1b}\text{R}^{1c}$, or $-\text{S}(\text{O})_2\text{NR}^{1b}\text{R}^{1c}$; or

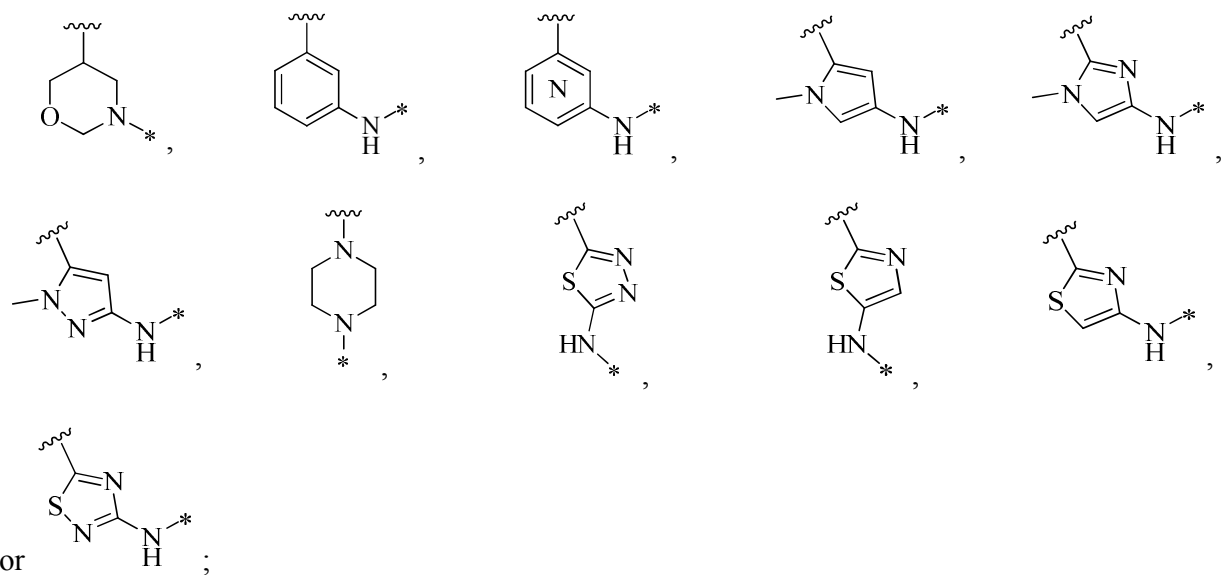
two R^L together, when there are two or more R^L attached to the same ring, are linked together to form (i) a bond, $-\text{O}-$, $-\text{NR}^N-$, or $-\text{S}-$; or (ii) C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, or C_{2-6} heteroalkenylene, each of which is optionally substituted with one or more substituents Q.

27. The compound of any one of claims 23 to 26, wherein r is 0.

28. The compound of claim 21, wherein L¹-L² is:

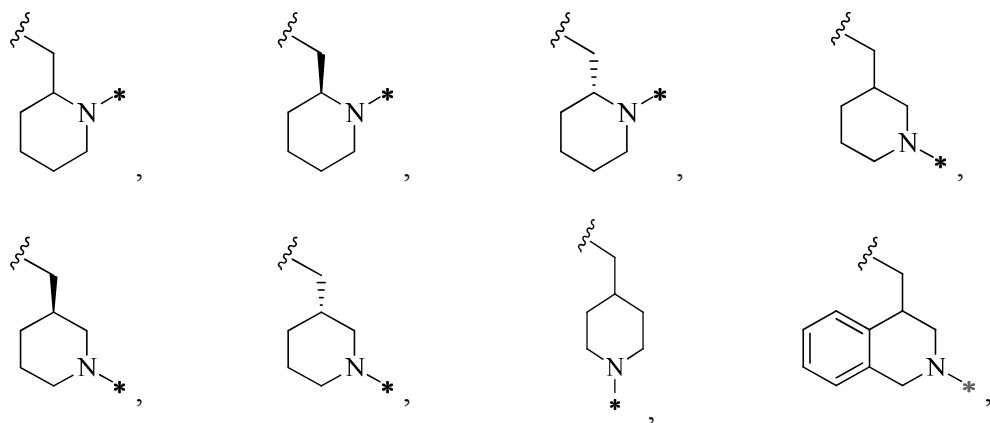


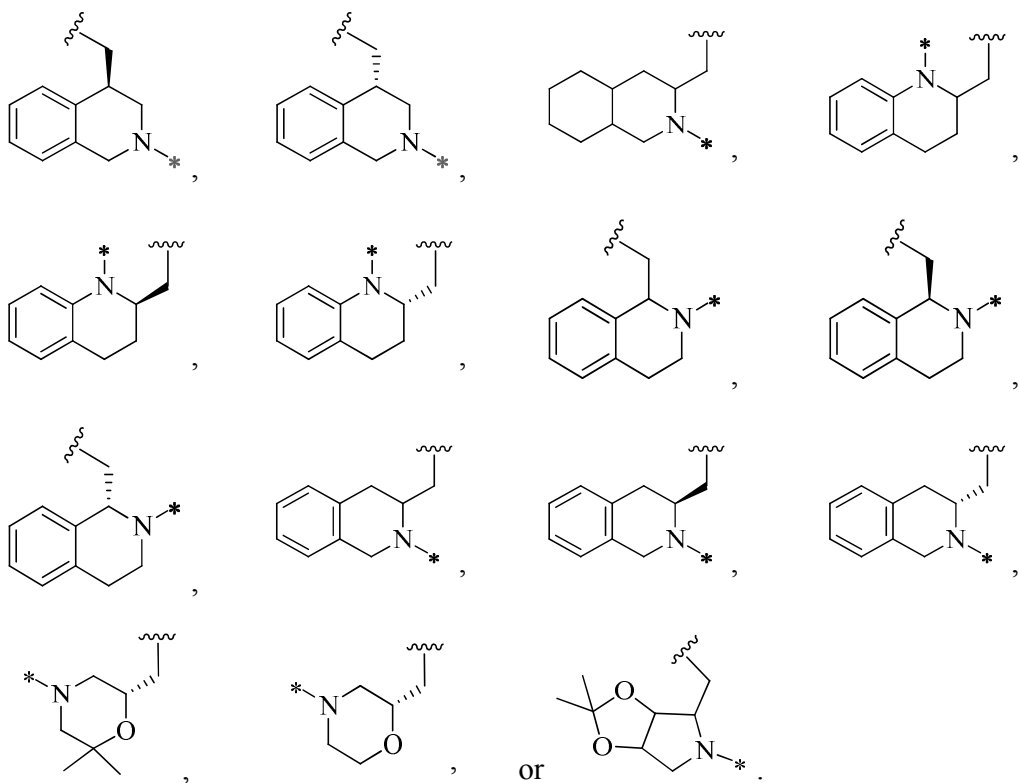




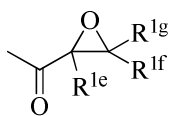
wherein the symbol  represents that the 6-membered ring contains one to three N atoms in the ring, and each sulfur is optionally oxidized as sulfoxide or sulfone.

29. The compound of claim 21, wherein L¹-L² is:

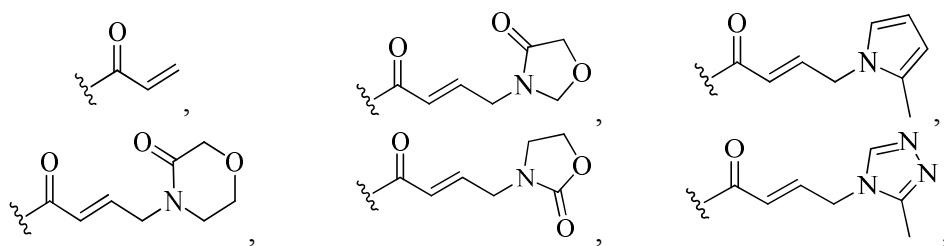


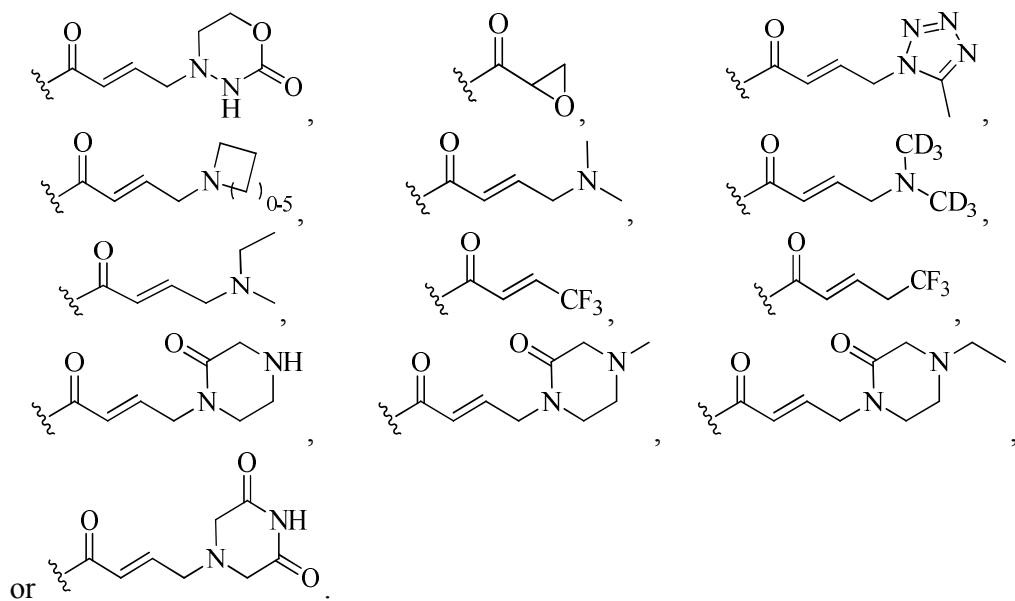


30. The compound of any one of claims 1 to 29, wherein R^1 is $-C(O)CR^{1e}=CR^{1f}R^{1g}$ or

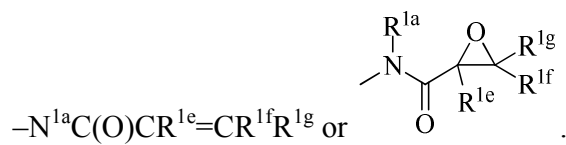


31. The compound of claim 30, wherein R^1 is selected from:

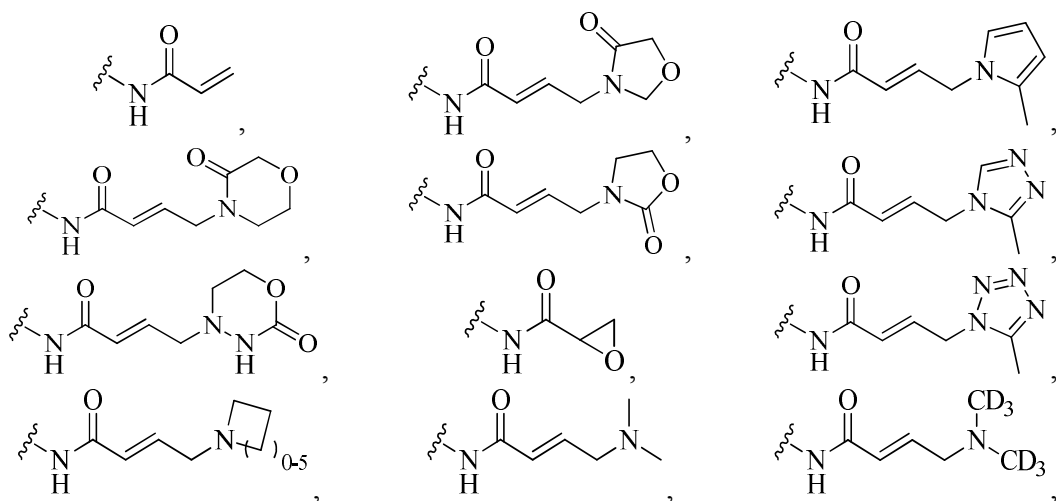


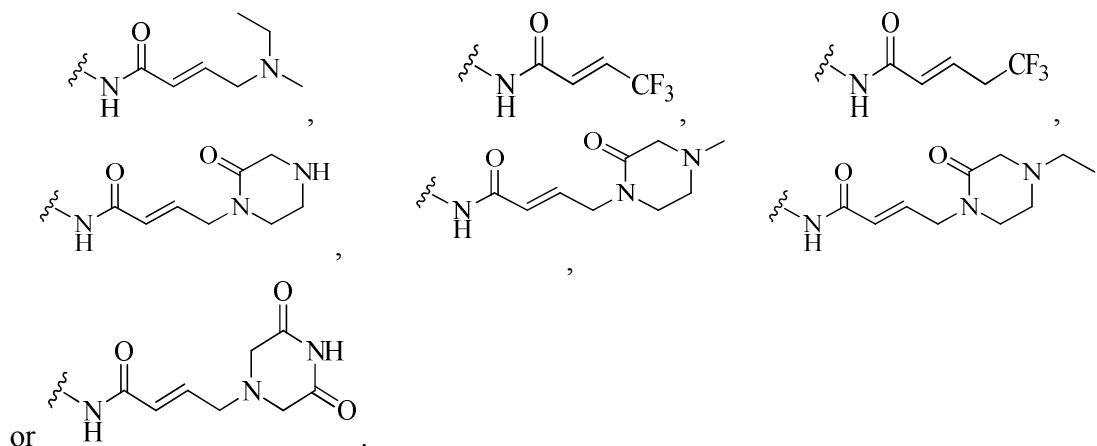


32. The compound of any one of claims 1 to 29, wherein R^1 is



33. The compound of claim 32, wherein R^1 is selected from:





34. The compound of any one of claims 1, 2, 5 to 10, and 13 to 33, wherein R^2 is C_{6-14} aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q.

35. The compound of claim 34, wherein R^2 is 6- to 10-membered monocyclic or bicyclic aryl, optionally substituted with one or more substituents Q.

36. The compound of claim 34, wherein R^2 is 5- to 10-membered monocyclic or bicyclic heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted with one or more substituents Q.

37. The compound of claim 34, wherein R^2 is 5- to 10-membered monocyclic or bicyclic heterocyclic comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted with one or more substituents Q.

38. The compound of claim 34, wherein R^2 is phenyl, pyridinyl, pyridazinyl, benzo[*c*][1,2,5]oxodiazolyl, or benzo[*c*][1,2,5]thiodiazolyl, each of which is optionally substituted with one or more substituents Q.

39. The compound of any one of claims 1 to 38, wherein R^4 is hydrogen.

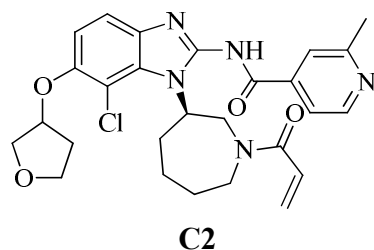
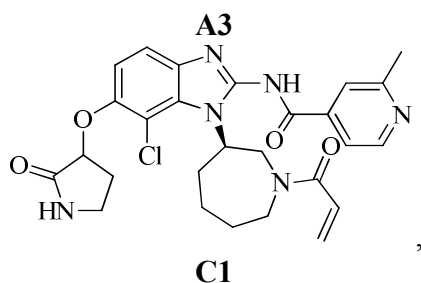
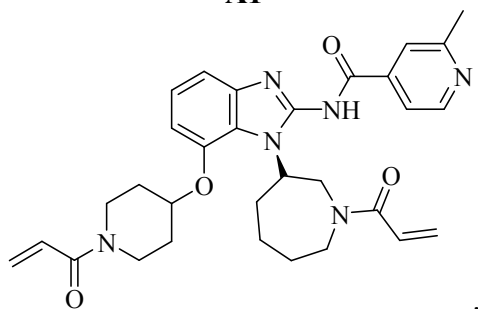
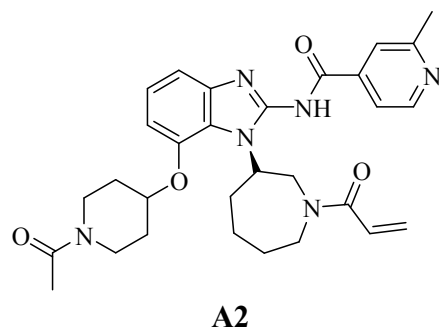
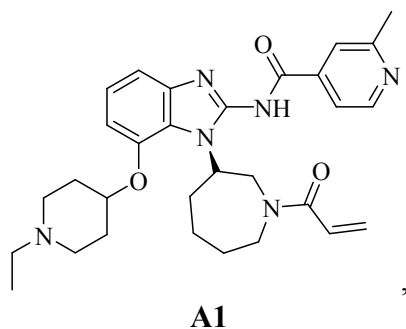
40. The compound of any one of claims 1 to 39, wherein R⁵ is hydrogen.

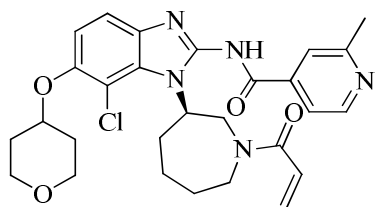
41. The compound of any one of claims 1 to 39, wherein R⁵ is -OR^{5a}, wherein R^{5a} is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q.

42. The compound of any one of claims 1 to 8 and 17 to 41, wherein R⁶ is hydrogen.

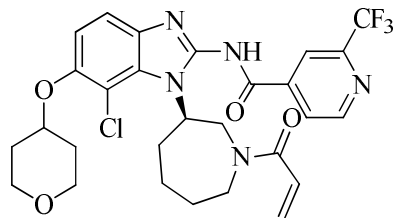
43. The compound of any one of claims 1 to 42, wherein Z is NH.

44. The compound of claim 1, selected from:

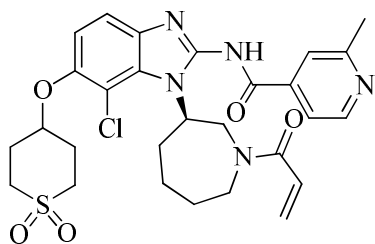




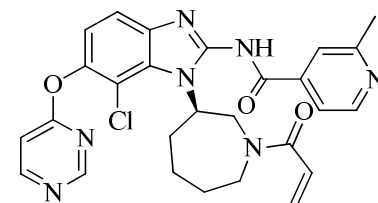
C3



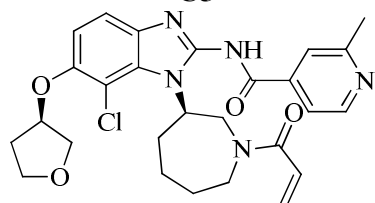
C4



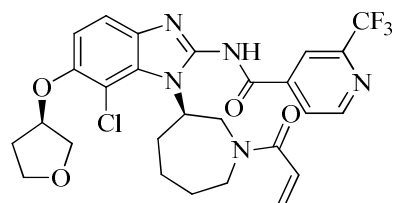
C5



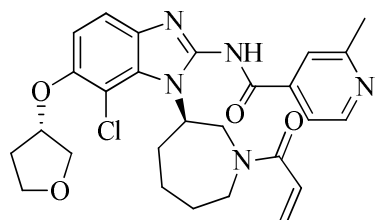
C6



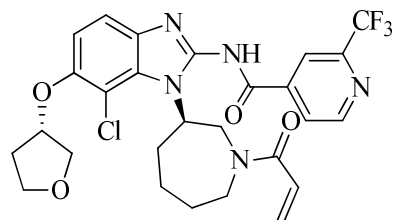
C7



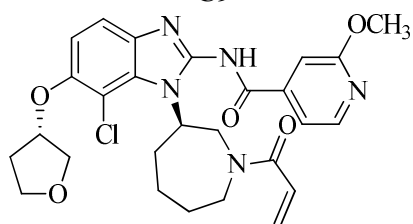
C8



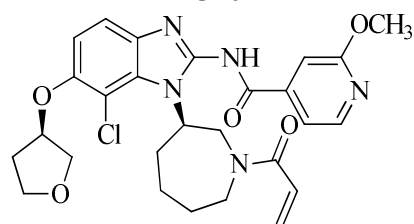
C9



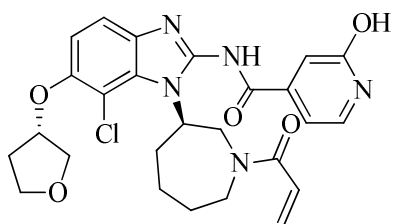
C10



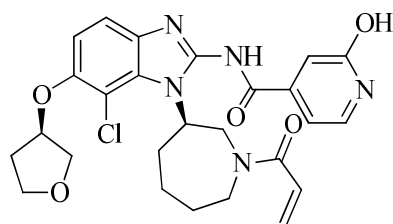
C11



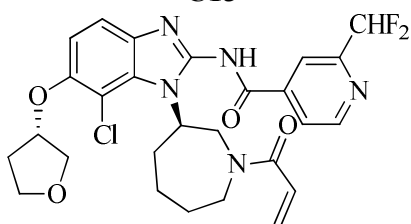
C12



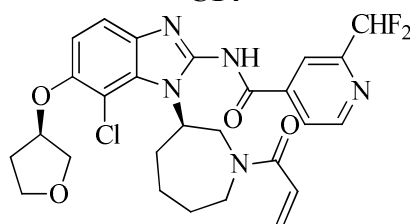
C13



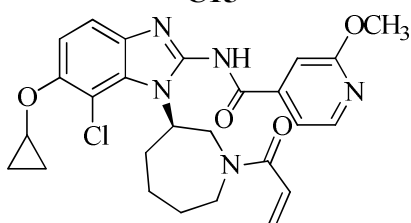
C14



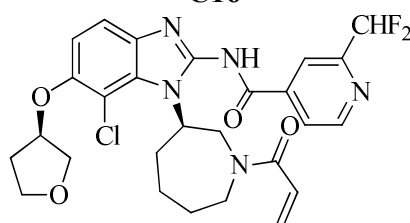
C15



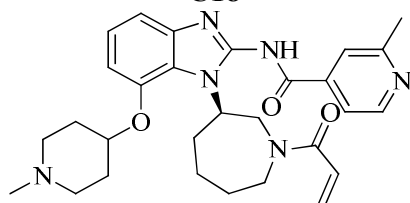
C16



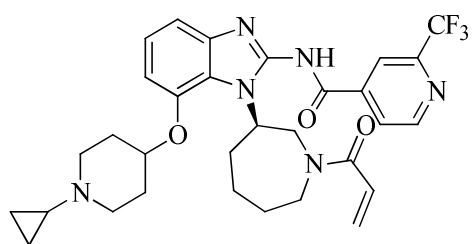
C17



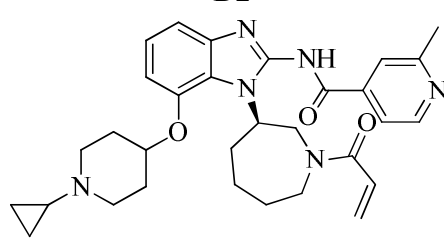
C18



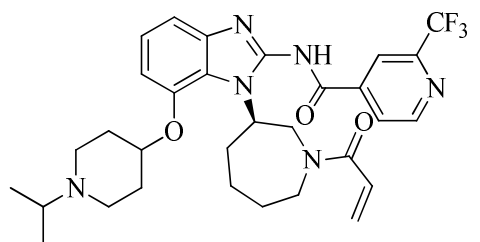
D2



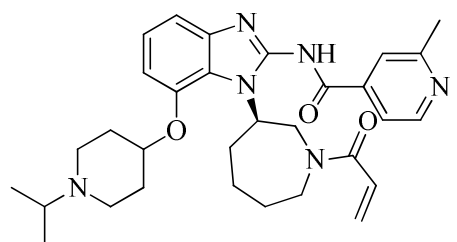
D3



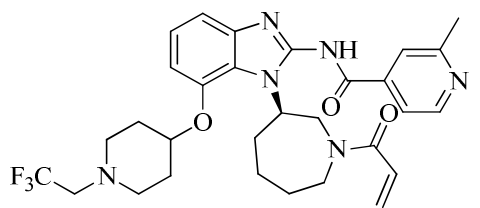
D4



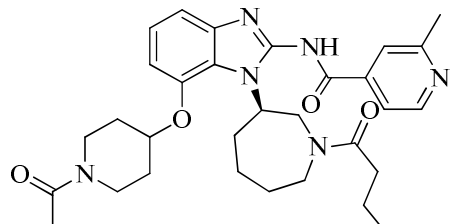
D5



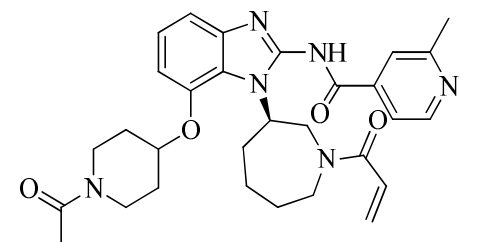
D6



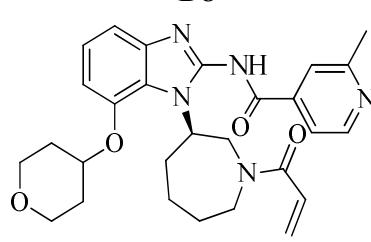
D7



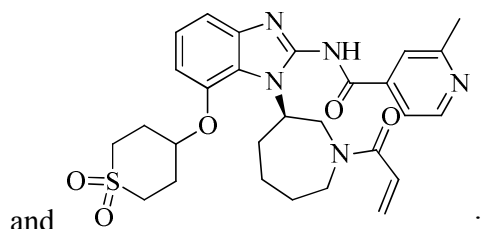
D8



D9



D10



D11

and single enantiomers, racemic mixtures, mixtures of diastereomers, and isotopic variants thereof; and pharmaceutically acceptable salts, and solvates thereof.

45. A pharmaceutical composition comprising the compound of any one of claims 1 to 44, and a pharmaceutically acceptable excipient.

46. The pharmaceutical composition of claim 45, wherein the composition is

formulated for oral, nasal, bronchial, or topical administration.

47. The pharmaceutical composition of claim 45 or 46, wherein the composition is formulated as a single dosage form.

48. The pharmaceutical composition of any one of claims 45 to 47, wherein the composition is formulated as oral, parenteral, nasal, respiratory, pulmonary, or intravenous dosage form.

49. The pharmaceutical composition of claim 48, wherein the pharmaceutical composition is in an oral dosage form.

50. The pharmaceutical composition of claim 49, wherein the oral dosage form is a tablet or capsule.

51. The pharmaceutical composition of any one of claims 45 to 50, further comprising a second therapeutic agent.

52. Use of a compound of any of claims 1 to 44 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of an ERBB-mediated condition, disorder, or disease.

53. The use of claim 52, wherein the ERBB-mediated condition, disorder, or disease is a proliferative disease.

54. Use of a compound of any of claims 1 to 44 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a proliferative disease.

55. The use of claim 53 or 54, wherein the proliferative disease is cancer.

56. The use of claim 55, wherein the cancer is drug-resistant.

57. The use of claim 55 or 56, wherein the cancer contains an ERBB variant.
58. The use of claim 57, wherein the ERBB variant is an EGFR variant.
59. The use of claim 58, wherein the EGFR variant contains one or more deletions, insertions, or substitutions at the amino acid positions of 689, 700, 709, 715, 719, 720, 746-759, 761-765, 767-775, 783, 784, 790, 796, 826, 839, 846, 858, 861, and 863.
60. The use of claim 58, wherein the EGFR variant contains one or more deletions, insertions, or substitutions at the amino acid positions of 719, 746-751, 790, and 858.
61. The use of claim 58, wherein the EGFR variant contains one, two, or more deletions, insertions, and/or substitutions, each independently selected from G719C, G719S, G719A, Δ E746-A750, Δ E746-T751, Δ E746-A750 (ins RP), Δ D761-E762 (ins EAFQ), Δ S768-D770 (dup SVD), Δ V769-D770 (ins ASV), Δ D770-N771 (ins SVQ), Δ P772-H773 (ins PR), Δ H773-V774 (ins NPH), Δ H773-V774 (ins H), Δ H773-V774 (ins PH), and Δ H773-V774 (ins GNPH), T790M, and L858R.
62. The use of claim 58, wherein the EGFR variant contains T790M, L858R, or a combination thereof.
63. The use of claim 57, wherein the ERBB variant is a HER2 variant.
64. The use of claim 63, wherein the HER2 is overexpressed in the cancer.
65. The use of any one of claims 55 to 64, wherein the cancer is resistant to an EGFR inhibitor.
66. The use of claim 65, wherein the cancer is resistant to afatinib, canertinib, dacomitinib, erlotinib, gefitinib, icotinib, lapatinib, neratinib, pelitinib, varlitinib, or a combination thereof.

67. The use of any one of claims 55 to 66, wherein the cancer is bladder cancer, brain tumor, breast cancer, cancer of the mouth and throat, colorectal cancer, lung cancer, or pancreatic cancer, prostate cancer, stomach cancer, or uterine cancer.

68. The use of claim 67, wherein the cancer is lung cancer.

69. The use of claim 67, wherein the cancer is non-small cell lung cancer.

70. The use of any one of claims 55 to 69, wherein the cancer is relapsed or refractory.

71. Use of a compound of any of claims 1 to 44 in the manufacture of a medicament for inhibiting the growth of a cell.

72. The use of claim 71, wherein the cell is cancer cell.

73. The use of claim 71 or 72, wherein the cell contains an ERBB variant.

74. The use of claim 73, wherein the ERBB variant is an EGFR variant.

75. The use of claim 74, wherein the EGFR variant contains one or more deletions, insertions, or substitutions at the amino acid positions of 689, 700, 709, 715, 719, 720, 746-759, 761-765, 767-775, 783, 784, 790, 796, 826, 839, 846, 858, 861, and 863.

76. The use of claim 74, wherein the EGFR variant contains one or more deletions, insertions, or substitutions at the amino acid positions of 719, 746-751, 790, and 858.

77. The use of claim 74, wherein the EGFR variant contains one, two, or more deletions, insertions, and/or substitutions, each independently selected from G719C, G719S, G719A, Δ E746-A750, Δ E746-T751, Δ E746-A750 (ins RP), Δ D761-E762 (ins EAFQ), Δ S768-D770 (dup SVD), Δ V769-D770 (ins ASV), Δ D770-N771 (ins SVQ), Δ P772-H773 (ins PR),

Δ H773-V774 (ins NPH), Δ H773-V774 (ins H), Δ H773-V774 (ins PH), and Δ H773-V774 (ins GNPH), T790M, and L858R.

78. The use of claim 74, wherein the EGFR variant contains T790M, L858R, or a combination thereof.

79. Use of a compound of any of claims 1 to 44 in the manufacture of a medicament for modulating the activity of an ERBB.

80. The use of claim 79, wherein the ERBB is an ERBB variant.

81. The use of claim 80, wherein the ERBB variant is an EGFR variant.

82. The use of claim 81, wherein the EGFR variant contains one or more deletions, insertions, or substitutions at the amino acid positions of 689, 700, 709, 715, 719, 720, 746-759, 761-765, 767-775, 783, 784, 790, 796, 826, 839, 846, 858, 861, and 863.

83. The use of claim 81, wherein the EGFR variant contains one or more deletions, insertions, or substitutions at the amino acid positions of 719, 746-751, 790, and 858.

84. The use of claim 81, wherein the EGFR variant contains one, two, or more deletions, insertions, and/or substitutions, each independently selected from G719C, G719S, G719A, Δ E746-A750, Δ E746-T751, Δ E746-A750 (ins RP), Δ D761-E762 (ins EAFQ), Δ S768-D770 (dup SVD), Δ V769-D770 (ins ASV), Δ D770-N771 (ins SVQ), Δ P772-H773 (ins PR), Δ H773-V774 (ins NPH), Δ H773-V774 (ins H), Δ H773-V774 (ins PH), and Δ H773-V774 (ins GNPH), T790M, and L858R.

85. The use of claim 81, wherein the EGFR variant contains T790M, L858R, or a combination thereof.