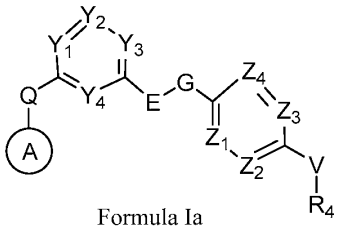
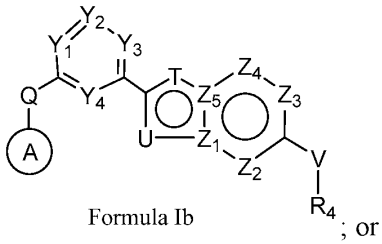
CLAIMS

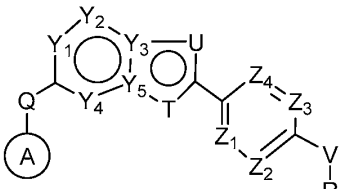
1. A compound of Formula Ia, Ib, or Ic,



Formula Ia ;



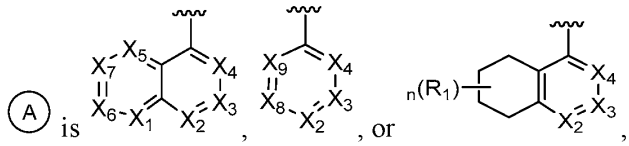
Formula Ib ; or



Formula Ic ;

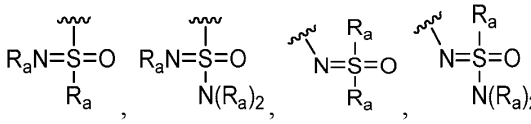
or a pharmaceutically acceptable salt thereof,

wherein:



A is , , or ,

each occurrence of X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, and X_9 are independently CR_1 or N;

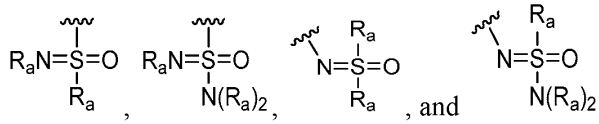
R_1 is selected from the group consisting of H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$,  and a partially saturated bicyclic heteroaryl optionally substituted by one or more $(C_1$-$C_6)$alkyl, halogenated $(C_1$-$C_6)$alkyl, $-SO_2R_a$, or $-SO_2N(R_a)_2$;

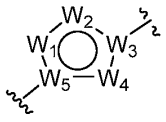
wherein the $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, aryl, and heteroaryl of R_1 are each optionally substituted by one or more $(C_1$-$C_6)$alkyl, halogenated $(C_1$-$C_6)$alkyl, halogen, $-OR_a$, $-CN$, or $-N(R_a)_2$;

n is an integer from 0-4 where valence permits;

Q is $C(R_a)_2$, O, NR_a, $N(C=O)R_a$, or NSO_2R_a;

Y_1, Y_2, Y_3, Y_4 and Y_5 are each independently N or CR_2 where valance permits;

R_2 is selected from the group consisting of H, halogen, D, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$,  ;

–E-G– is $-(C=O)NR_x-$, $-NR_x(C=O)-$, $-N(R_x)(C=O)N(R_x)-$, $-O(C=O)N(R_x)-$, $-N(R_x)(C=O)O-$, $-SO_2NR_x-$, $-NR_xSO_2-$, or  ; wherein;

each occurrence of R_x is independently H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, aryl, or heteroaryl; or wherein R_x and Y_3, R_x and Y_4, R_x and Z_1, or R_x and Z_4 taken together form an optionally substituted 5-6-membered heterocycle;

W_1, W_2, W_3, W_4, and W_5 are each independently CR_6, N, or NR_6 where valence permits;

each occurrence of R_6 is independently selected from the group consisting of H, halogen, $(C_1$-$C_6)$alkyl, and $(C_1$-$C_6)$haloalkyl;

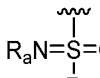
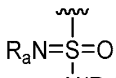
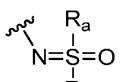
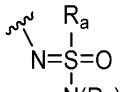
each occurrence of T is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits;

each occurrence of U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits;

each occurrence of R_b is independently H or $(C_1$-$C_6)$alkyl;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently N or CR_3 where valance permits;

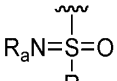
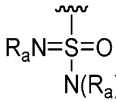
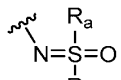
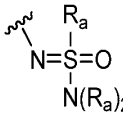
R_3 is selected from the group consisting of H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, aryl, heteroaryl, –

OR_a, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$,  ,  ,  , and  ;

V is absent, $C(R_a)_2$, NR_a, $N(C=O)R_a$, NSO_2R_a or O;

R_4 is selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, aryl, and heteroaryl, each optionally substituted with one or more R_5;

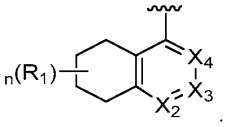
or alternatively V and R_4 taken together form a $(C_3$-$C_7)$heterocycloalkyl or $(C_4$-$C_{10})$heterospiroalkyl;

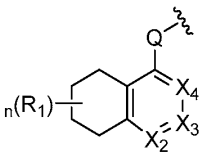
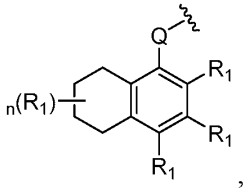
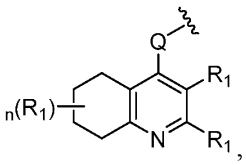
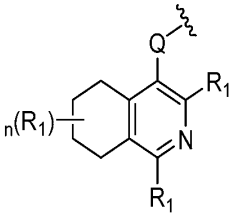
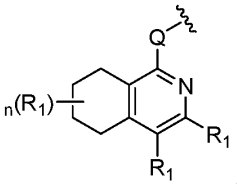
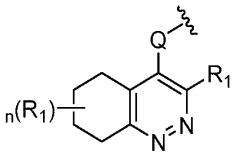
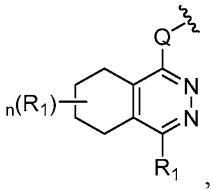
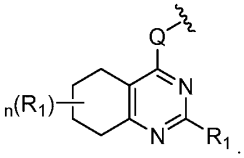
each occurrence of R_5 is independently selected from the group consisting of H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$, $N(R_a)COR_a$,  ,  ,  , and  ; and

each occurrence of R_a is independently H, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_3$-$C_7)$cycloalkyl, aryl, or heteroaryl, or two R_a taken together form a 4-6-membered ring optionally substituted with halogen or $(C_1$-$C_6)$alkyl.

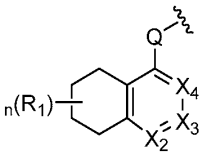
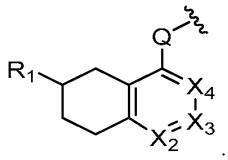
2. The compound of claim 1, wherein Q, T, and U are each independently O, NH, NCH_3, N(C=O)H, $N(C=O)CH_3$, $N(C=O)CH_2CH_3$, NSO_2CH_3, or $NSO_2CH_2CH_3$.

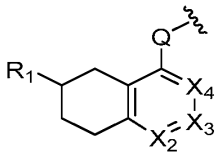
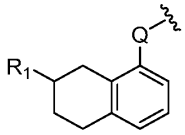
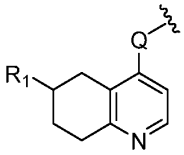
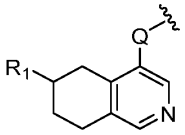
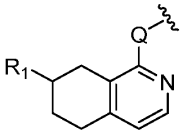
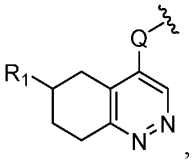
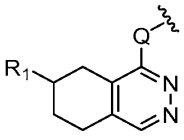
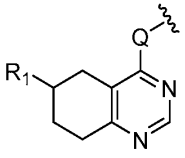
3. The compound of claim 1 or 2, wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, Y_1, Y_2, Y_3, Y_4, Y_5, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CH or N.

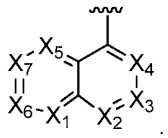
4. The compound of any one of claims 1-3, wherein (A) is  .

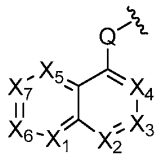
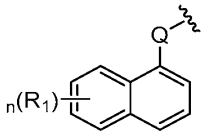
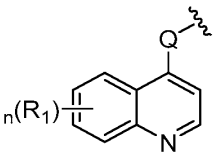
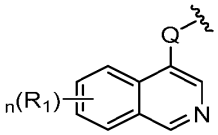
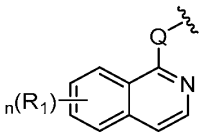
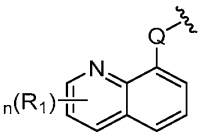
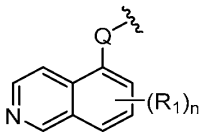
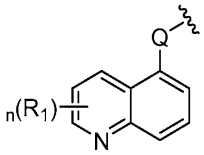
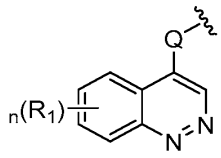
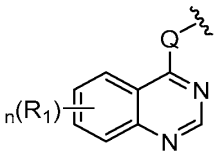
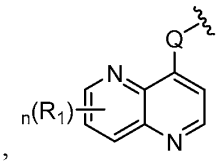
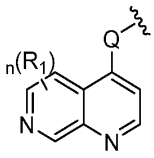
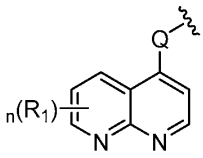
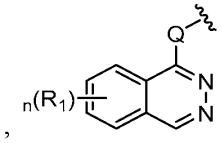
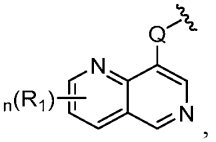
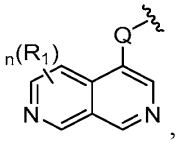
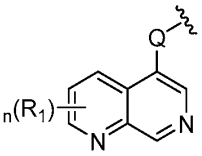
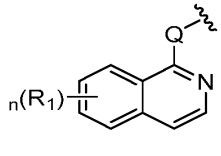
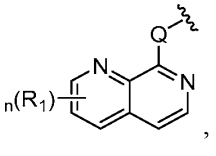
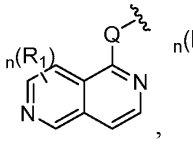
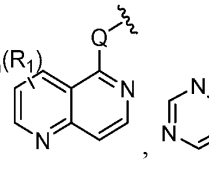
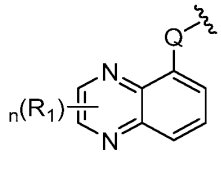
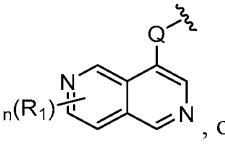
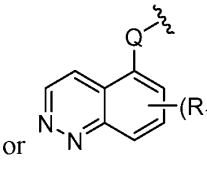
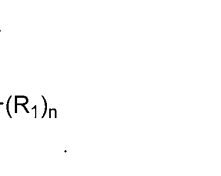
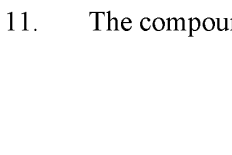
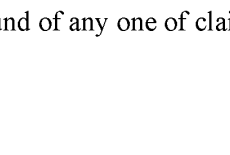
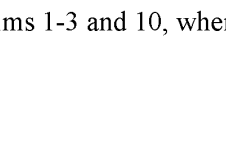
5. The compound of any one of claims 1-4, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

6. The compound of any one of claims 1-5, wherein n is 0, 1, or 2.

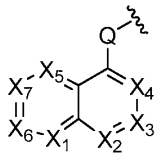
7. The compound of any one of claims 1-6, wherein the structural moiety  has the structure of  .

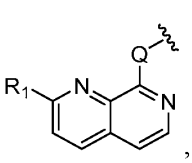
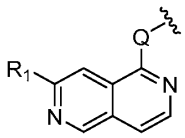
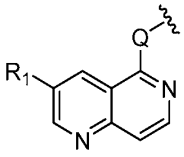
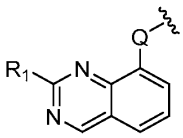
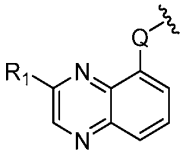
8. The compound of claim 7, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

9. The compound of any one of claims 1-3, wherein Ⓐ is  .

10. The compound of any one of claims 1-3 and 9, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  , or  .

11. The compound of any one of claims 1-3 and 10, wherein n is 0, 1, or 2.

12. The compound of any one of claims 1-3 and 9-11, wherein the structural moiety  has the structure of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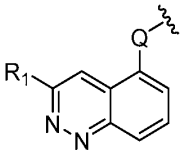
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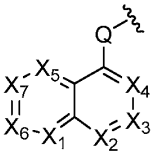
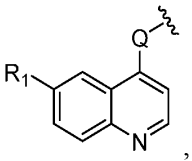
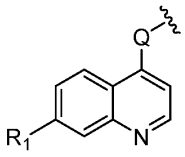
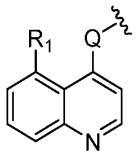
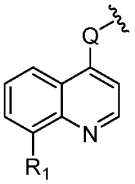
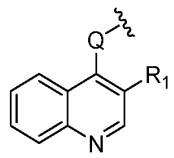
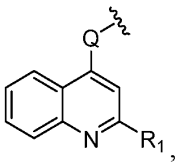
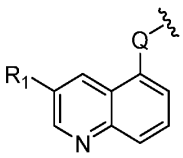
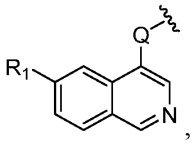
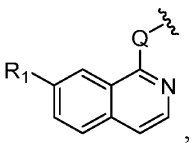
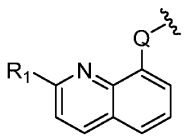
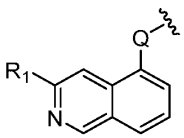
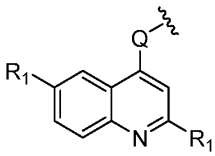
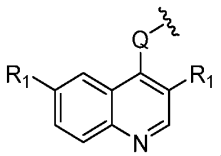
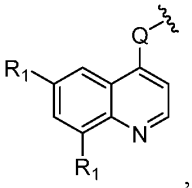
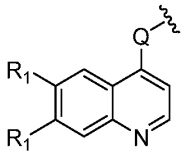
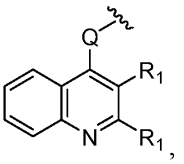
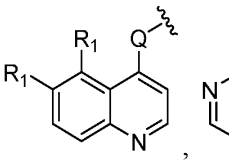
13. The compound of any one of claims 1-3 and 9-12, wherein the structural moiety

has the structure of

















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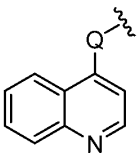
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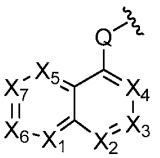
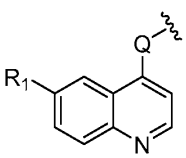
14. The compound of any one of claims 1-3 and 9-12, wherein the structural moiety

has the structure of

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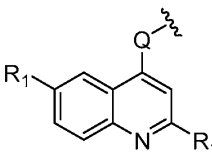
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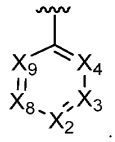
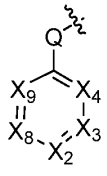
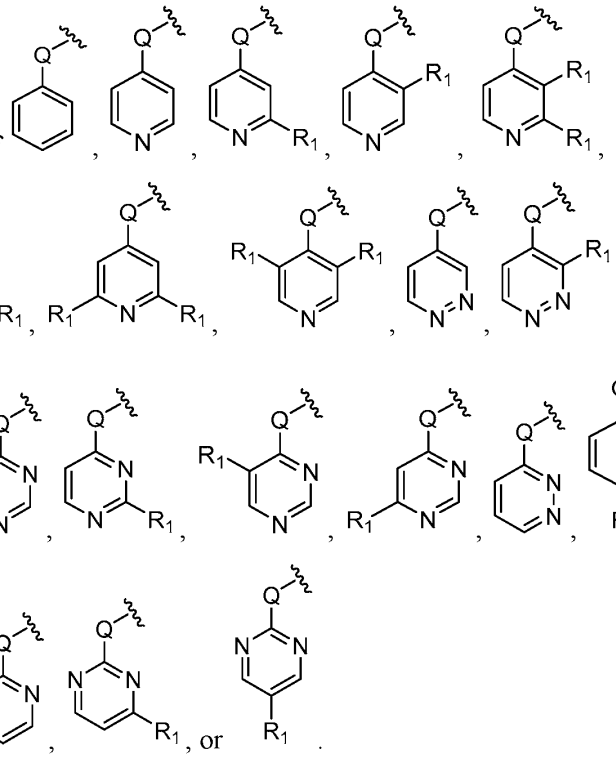
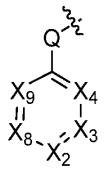
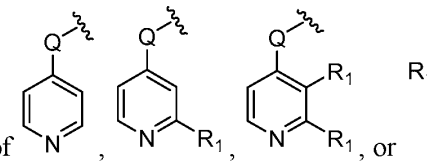
15. The compound of any one of claims 1-3, wherein  is  .

16. The compound of any one of claims 1-3 and 15, wherein the structural moiety  has the structure of  .

17. The compound of any one of claims 1-3 and 15-16, wherein the structural moiety  has the structure of  .

18. The compound of any one of claims 1-17, wherein Q is O.

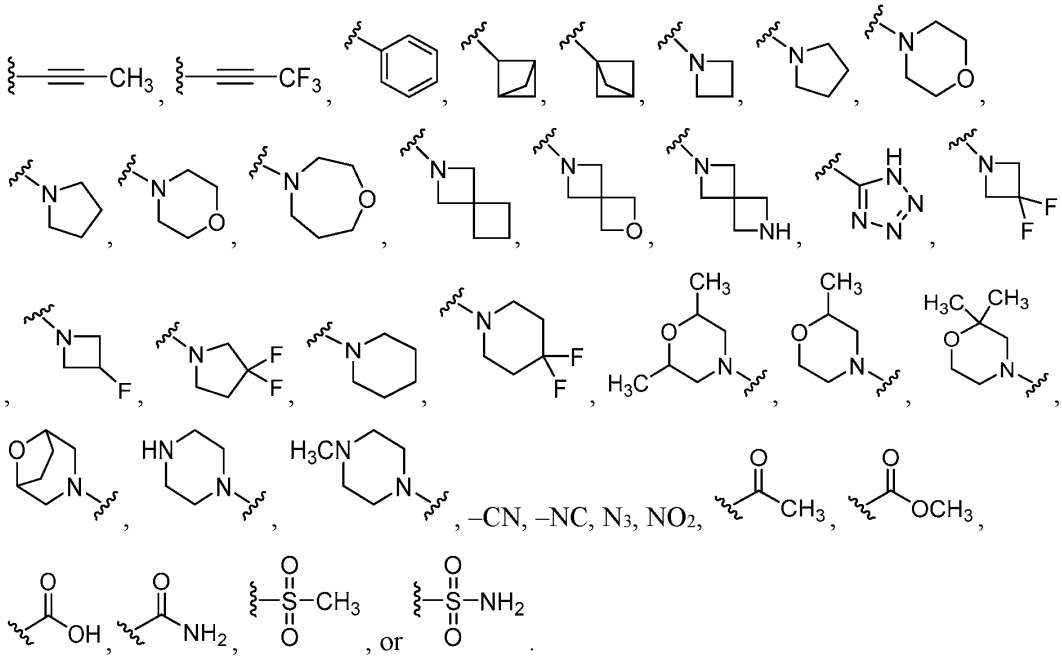
19. The compound of any one of claims 1-17, wherein Q is NR_a, $N(C{=}O)R_a$, or NSO_2R_a.

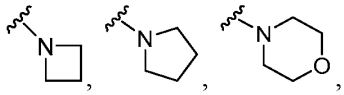
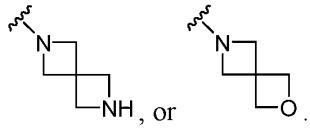
20. The compound of any one of claims 1-19, wherein each occurrence of R_1 is independently H, D, halogen, OR_a, $N(R_a)_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, aryl,

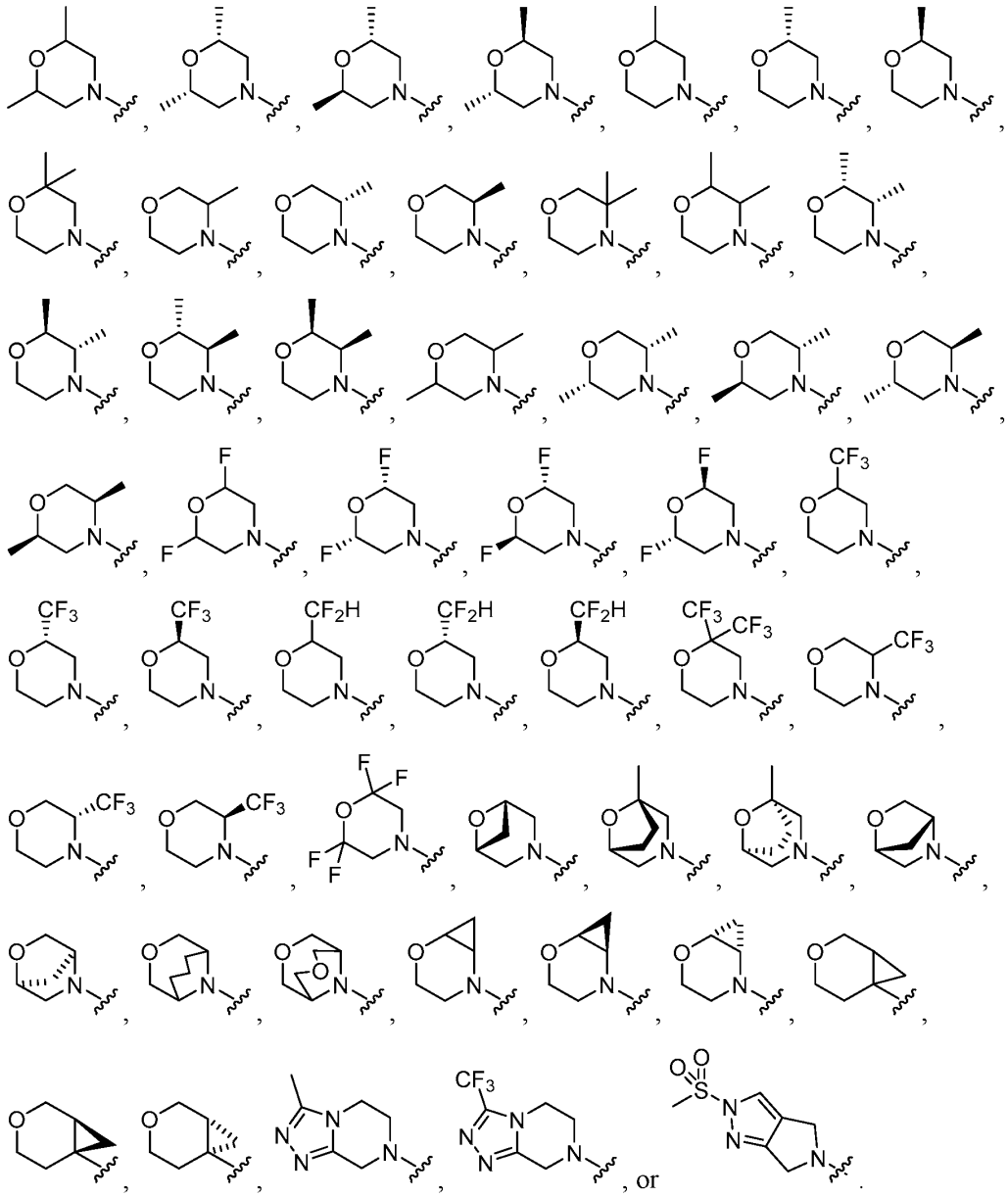
$(C_4\text{-}C_{10})$bicycloalkyl, –CN, –NC, N_3, NO_2, COR_a, CO_2R_a, $CON(R_a)_2$, $–SO_2R_a$, or $–SO_2N(R_a)_2$; wherein the $(C_3\text{-}C_7)$heterocycloalkyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl.

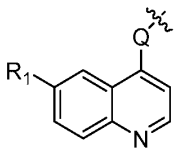
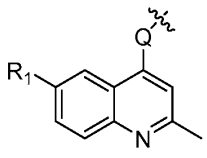
21. The compound of any one of claims 1-20, wherein each occurrence of R_1 is independently H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $N(R_a)_2$, or –CN; wherein the $(C_3\text{-}C_7)$heterocycloalkyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl.

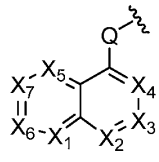
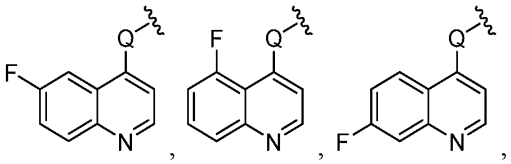
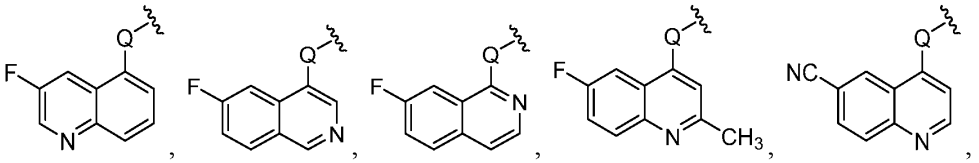
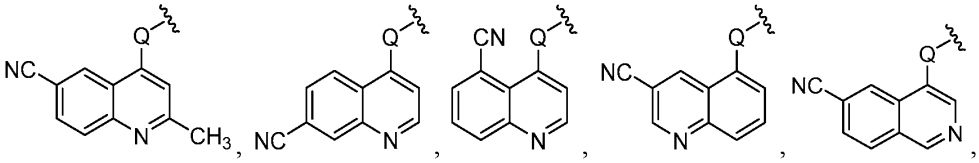
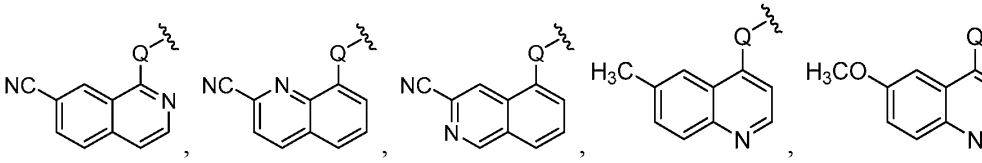
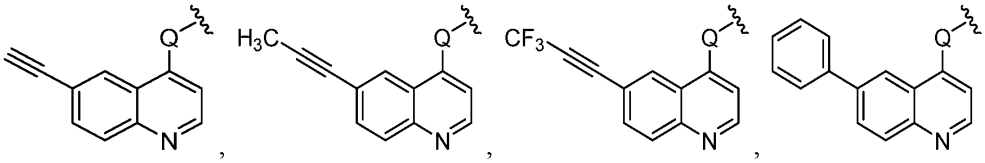
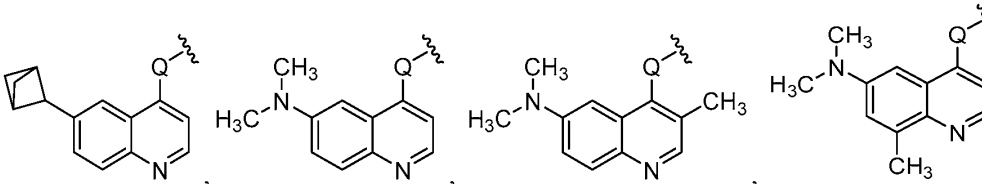
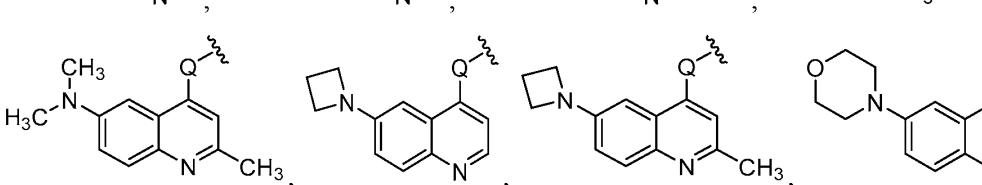
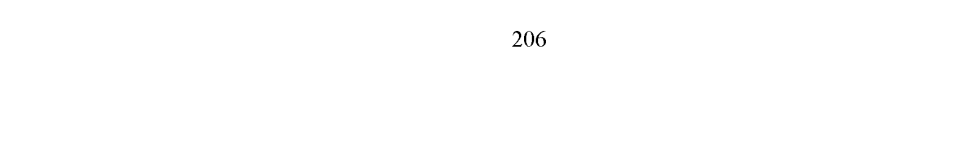
22. The compound of any one of claims 1-21, wherein each occurrence of R_1 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, or $(C_3\text{-}C_7)$heterocycloalkyl; wherein the $(C_3\text{-}C_7)$heterocycloalkyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl.

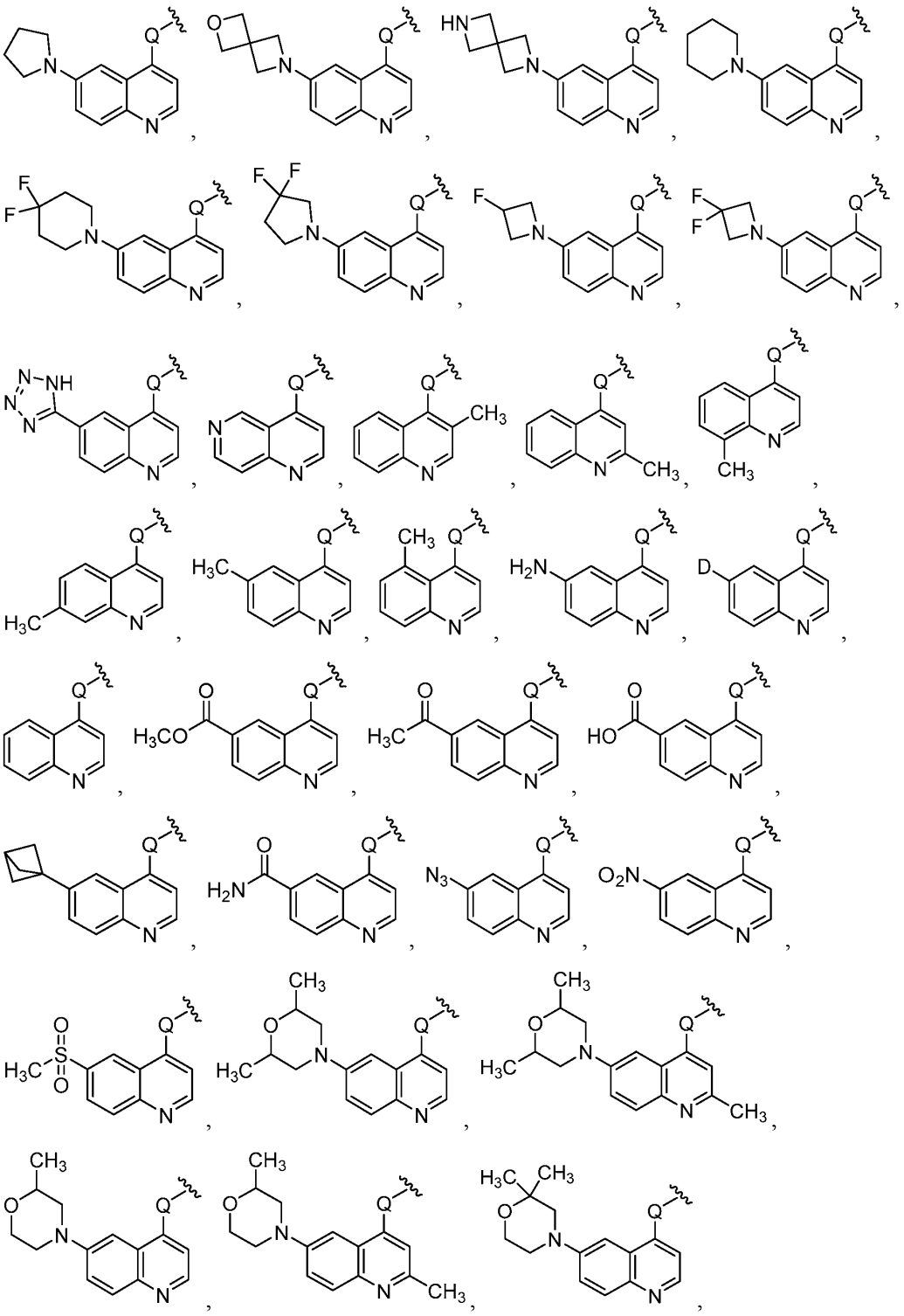
23. The compound of any one of claims 1-22, wherein each occurrence of R_1 is independently H, D, F, Cl, Br, CH_3, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$,  ,  , –CN, –NC, N_3, NO_2, , , or .

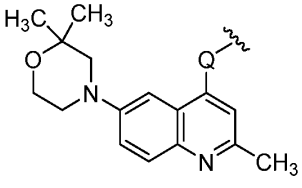
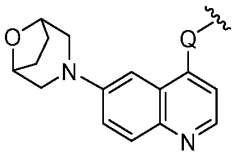
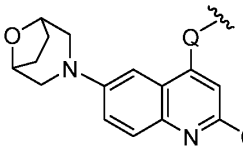
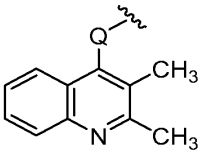
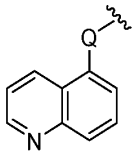
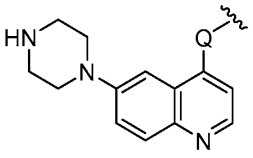
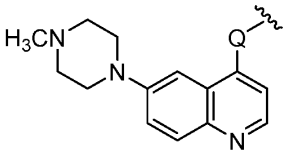
24. The compound of any one of claims 1-23, wherein each occurrence of R_1 is independently H, D, F, CH_3, NH_2, $NHCH_3$, $N(CH_3)_2$,  ,  , or .

25. The compound of any one of claims 1-21, wherein at least one occurrence of R_1 is  , or .

26. The compound of claim 25, wherein (A) is  or  .

27. The compound of any one of claims 1-3, 10-14, and 18-24, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  , ,  .

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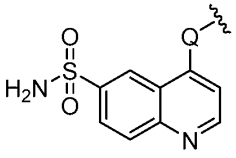
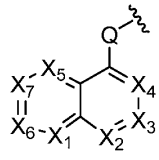
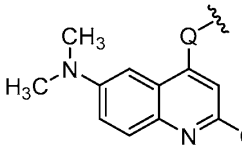
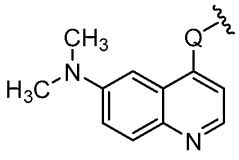

, wherein Q is O or NH.

28. The compound of any one of claims 1-3, 10-14, 18-25 and 27, wherein the structural moiety  has the structure of 

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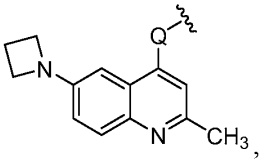
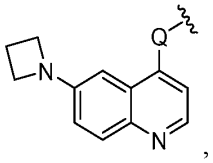
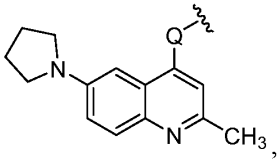
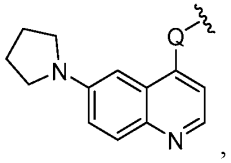
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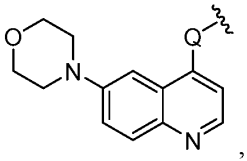
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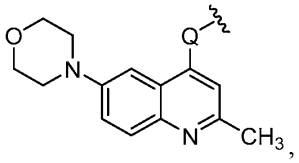
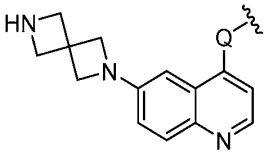
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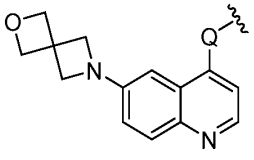
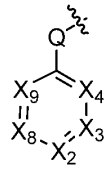
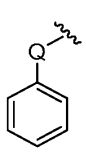

, wherein Q is O or NH.

29. The compound of any one of claims 1-3 and 15-24, wherein the structural moiety


has the structure of

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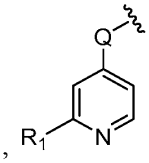
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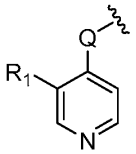
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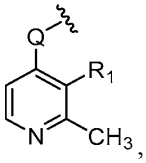
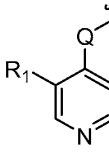
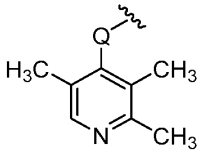
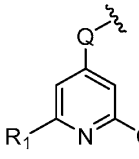
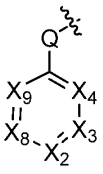
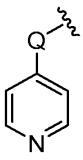
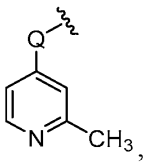
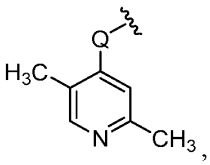
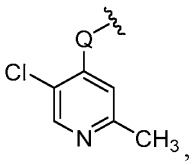
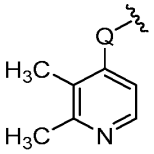
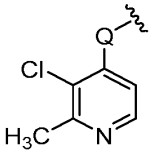
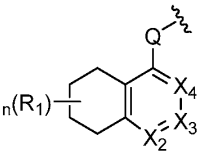
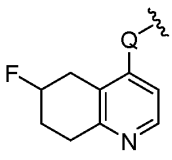
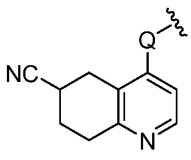
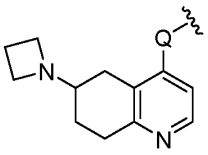
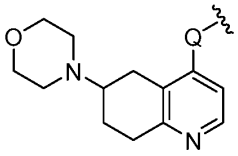
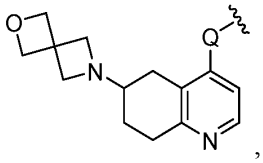
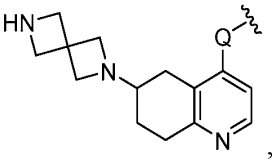
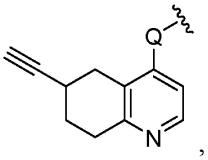
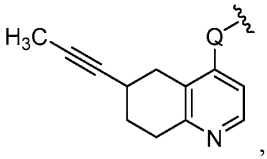
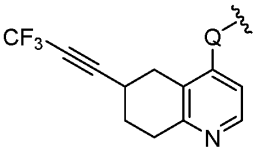
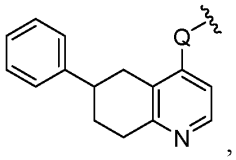
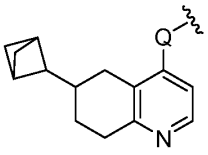
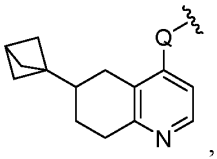
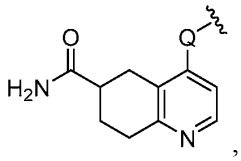
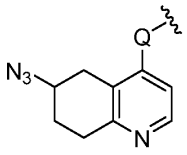
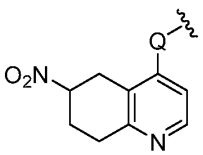
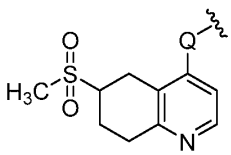
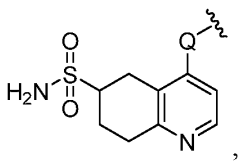
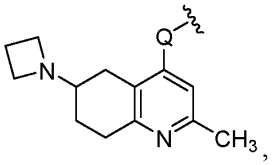
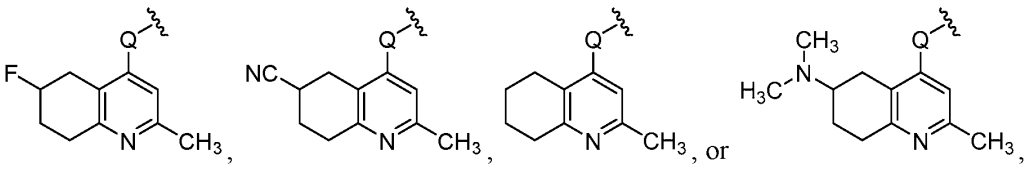


 ,  , or  , wherein Q is O or NH and R_1 is H, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, halogenated (C_3-C_7)heterocycloalkyl, or halogen.

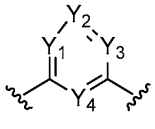
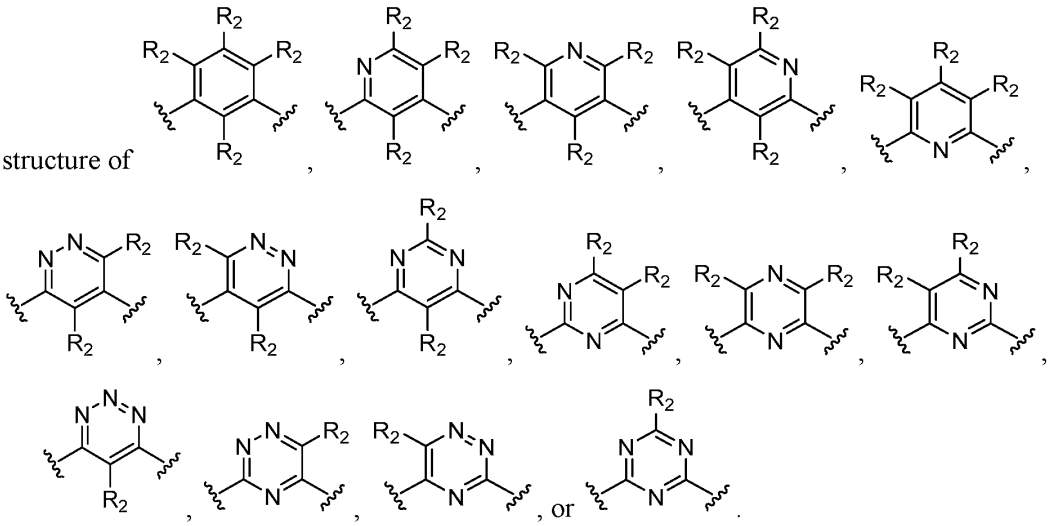
30. The compound of any one of claims 1-3, 15-24, and 29, wherein the structural moiety  has the structure of  ,  ,  ,  ,  , or  wherein Q is O or NH.

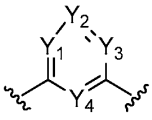
31. The compound of any one of claims 1-3, 5-8, and 14-19, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .



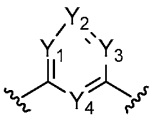
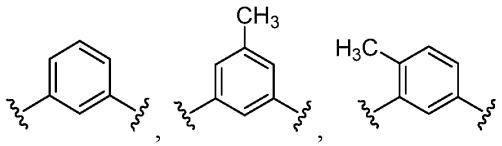
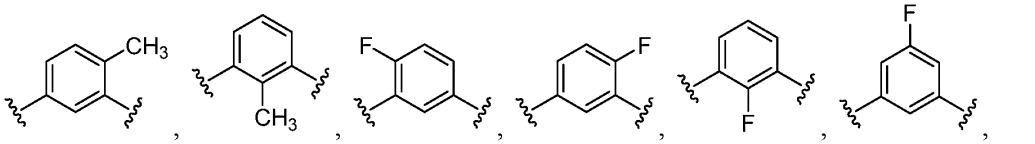
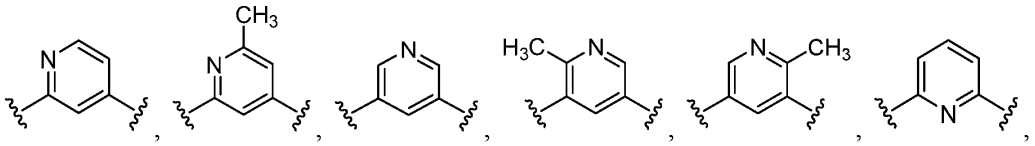
wherein Q is O or NH.

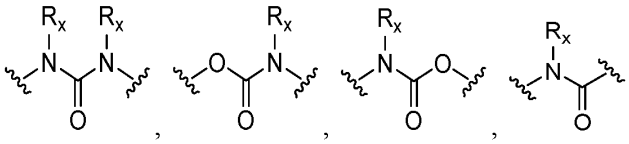
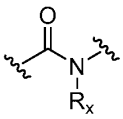
32. The compound of claim 1, having the formula of Formula Ia.

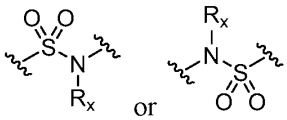
33. The compound of claim 1 or 32, wherein the structural moiety  has the structure of 

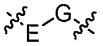
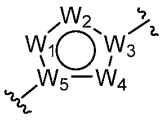
34. The compound of any one of claims 1 and 32-33, wherein the structural moiety  has the structure of

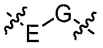
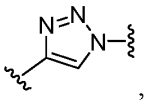
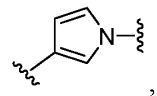
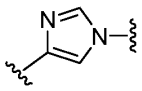
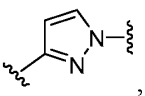
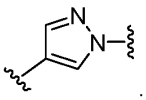
35. The compound of any one of claims 1 and 32-34, wherein each occurrence of R_2 is independently H, halogen, CH_3, CF_3, OH, NH_2, –$NHCH_3$, or –$N(CH_3)_2$.

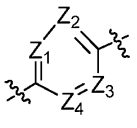
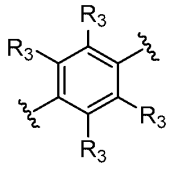
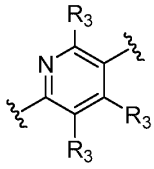
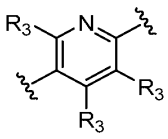
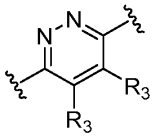
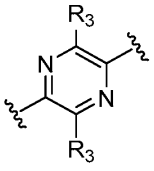
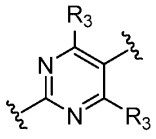
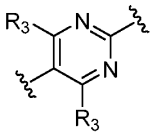
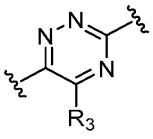
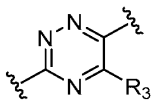
36. The compound of any one of claims 1 and 32-35, wherein the structural moiety  has the structure of  ,  ,  ,  , or .

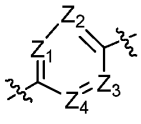
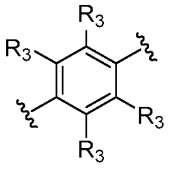
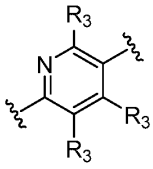
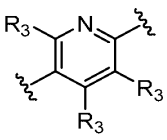
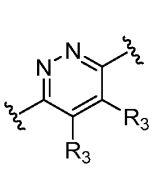
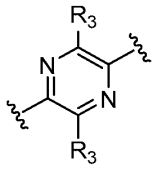
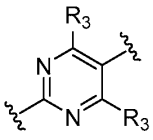
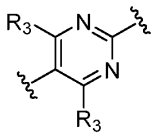
37. The compound of any one of claims 1 or 32-36, wherein the structural moiety has the structure of  , or  .

38. The compound of any one of claims 1 or 32-36, wherein the structural moiety has the structure of  .

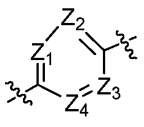
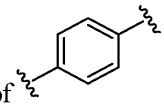
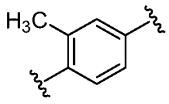
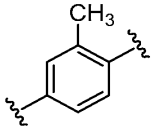
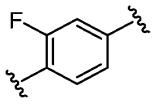
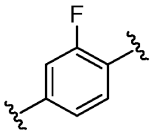
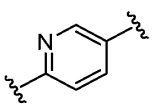
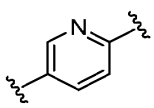
39. The compound of any one of claims 1 or 32-36, wherein the structural moiety  has the structure of  .

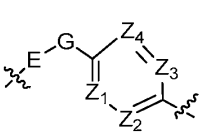
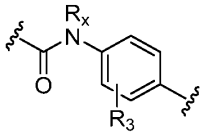
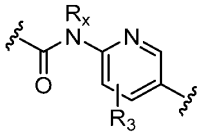
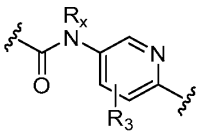
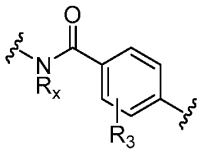
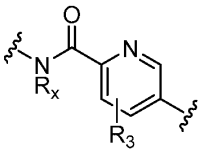
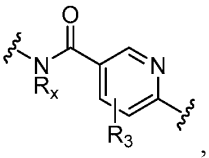
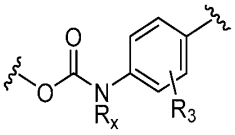
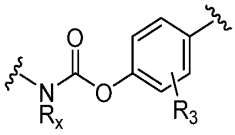
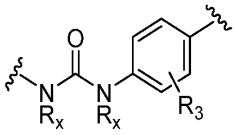
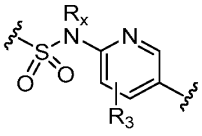
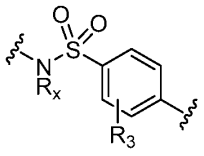
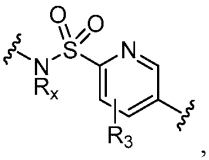
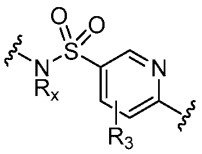
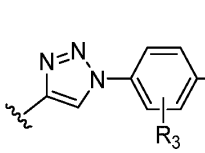
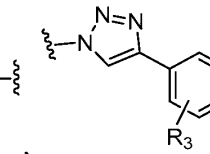
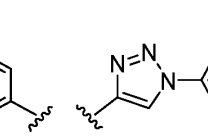
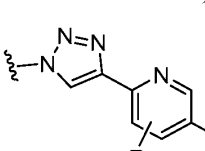
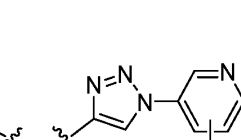
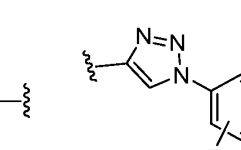
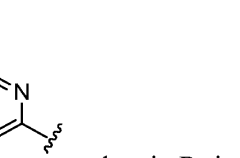
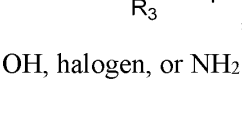
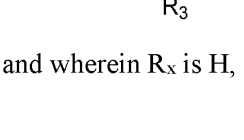
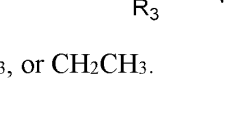
40. The compound of any one of claims 1, 32-36, and 39, wherein the structural moiety  has the structure of  ,  ,  ,  , or  .

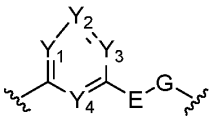
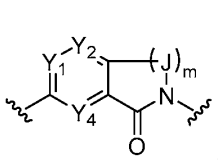
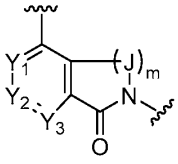
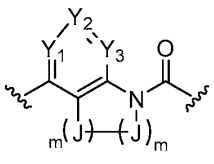
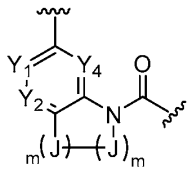
41. The compound of any one of claims 1 and 32-40, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  , or  .

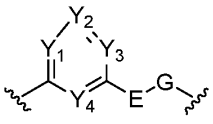
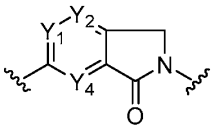
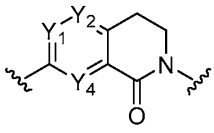
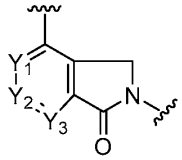
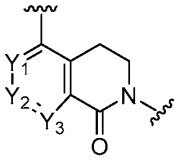
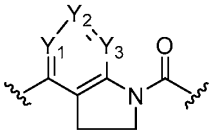
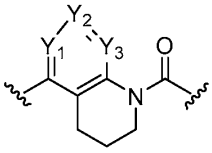
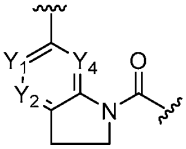
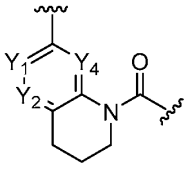
42. The compound of any one of claims 1 and 32-41, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

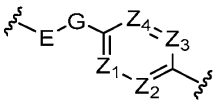
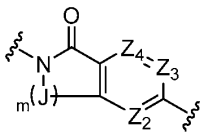
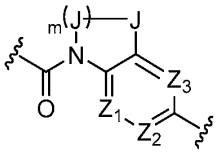
43. The compound of any one of claims 1 and 32-42, wherein each occurrence of R_3 is H, halogen, CH_3, CF_3, OH, NH_2, –$NHCH_3$, or –$N(CH_3)_2$.

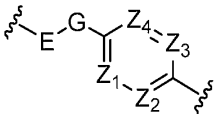
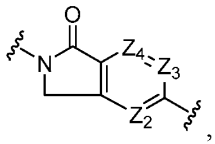
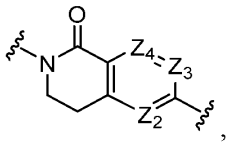
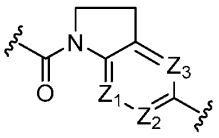
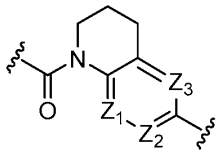
44. The compound of any one of claims 1 and 32-43, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

45. The compound of any one of claims 1 and 32-44, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_X is H, CH_3, or CH_2CH_3.

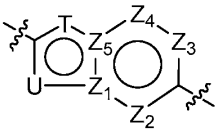
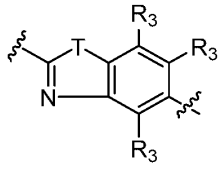
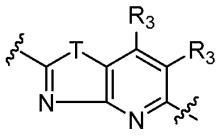
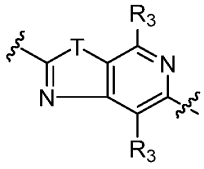
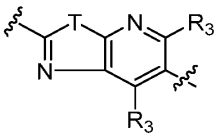
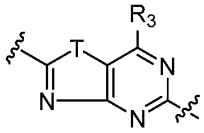
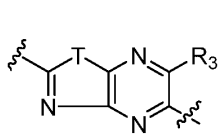
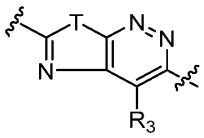
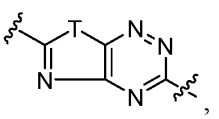
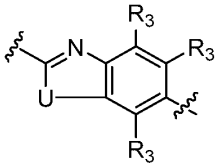
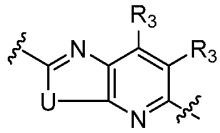
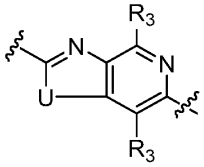
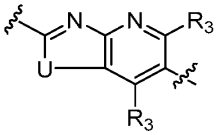
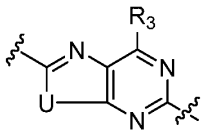
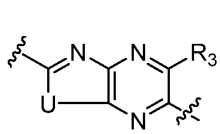
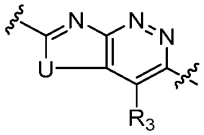
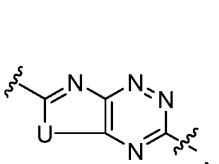
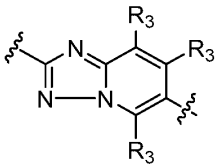
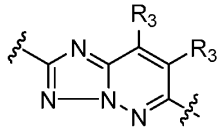
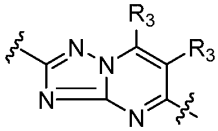
46. The compound of claim 1 or 32, wherein the structural moiety  has the structure of  ,  ,  , or  , wherein each occurrence of m is independently 1 or 2, J is $C(R_y)_2$, and each occurrence of R_y is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen.

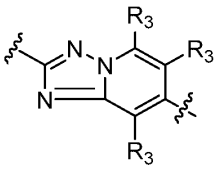
47. The compound of any one of claims 1, 32, and 46, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  , or  , wherein Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF.

48. The compound of claim 1 or 32, wherein the structural moiety  has the structure of  or  , wherein each occurrence of m is independently 1 or 2, J is $C(R_z)_2$, and each occurrence of R_z is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen.

49. The compound of any one of claims 1, 32, and 48, wherein the structural moiety  has the structure of  ,  ,  , or  , wherein Z_1, Z_2, Z_3, and Z_4 are each independently N, CH, CCH_3, or CF.

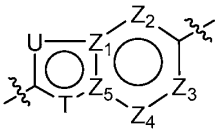
50. The compound of claim 1, having the formula of Formula Ib.

51. The compound of claim 1 or 50, wherein the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or

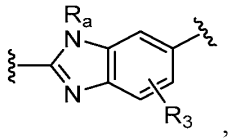


, wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

52. The compound of any one of claims 1 and 50-51, wherein the structural moiety



has the structure of



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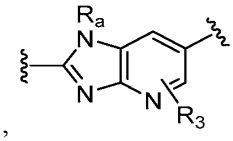

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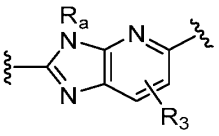

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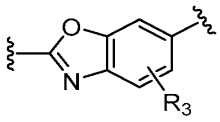

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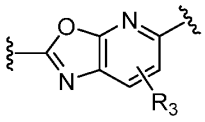

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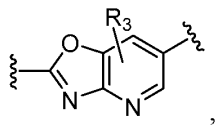

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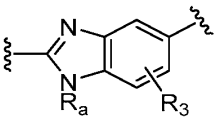

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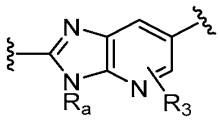

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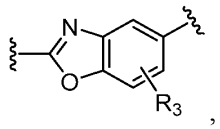

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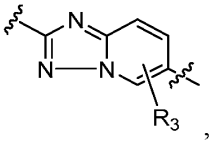

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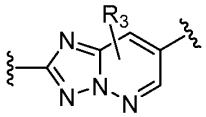

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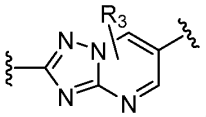

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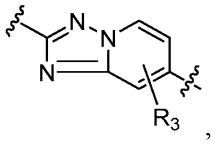
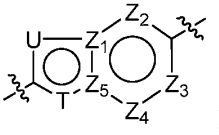


, wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_a is H, CH_3, or CH_2CH_3.

53. The compound of any one of claims 1 and 50-51, wherein the structural moiety



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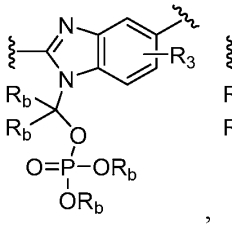

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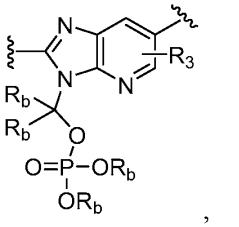

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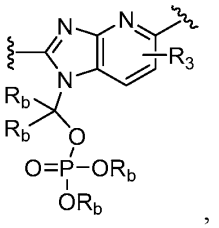

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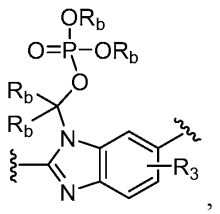

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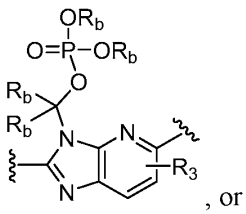

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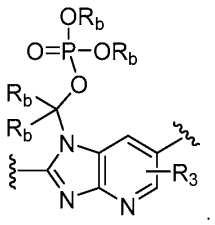


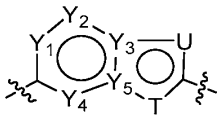
.

54. The compound of claim 49 or 51, wherein each occurrence of R_b is independently H or $(C_1\text{-}C_6)$alkyl.

55. The compound of claim 53 or 54, wherein each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

56. The compound of claim 1, having the formula of Formula Ic.

57. The compound of claims 1 or 56, wherein the structural moiety



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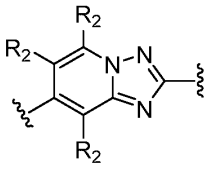
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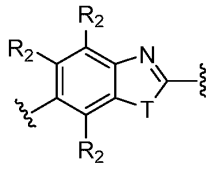
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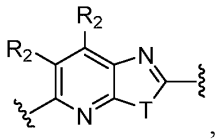
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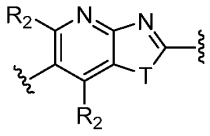
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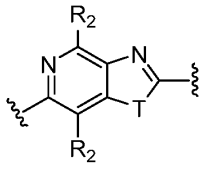
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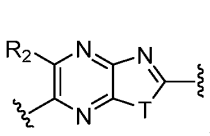
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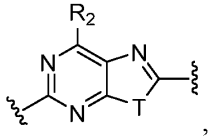
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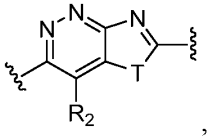
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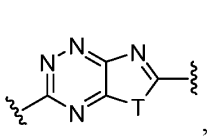
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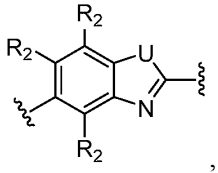
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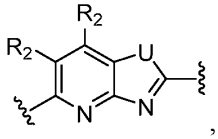
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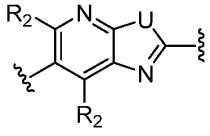
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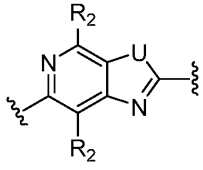
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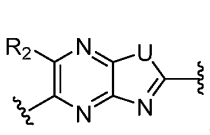
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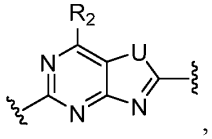
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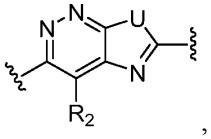
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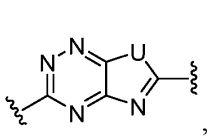
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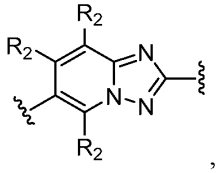
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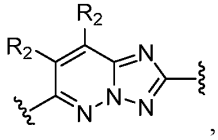
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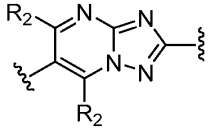
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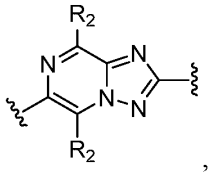
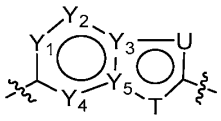
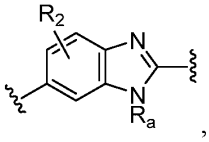
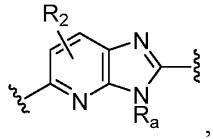
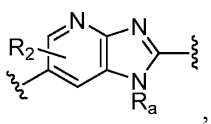
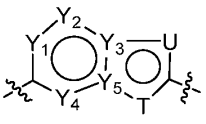
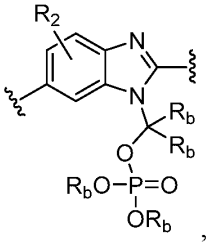
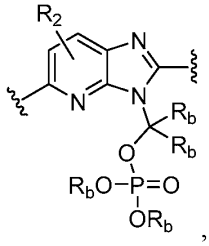
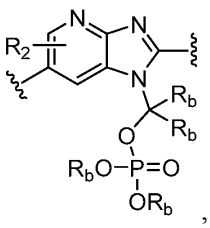
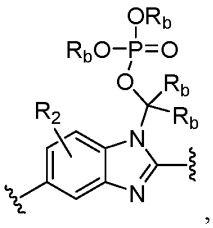
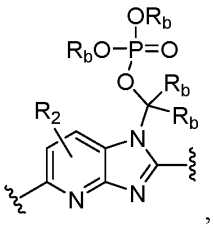
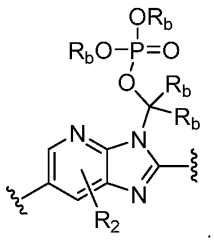

, wherein each occurrence of T and U is independently O, N, NR_a, $N(C{=}O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

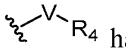
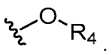
58. The compound of any one of claims 1 and 56-57, wherein the structural moiety  has the structure of  ,  ,  ,

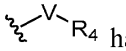
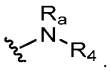
59. The compound of any one of claims 1 and 56-57, wherein the structural moiety  has the structure of  ,  ,  ,  ,  , or  .

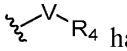
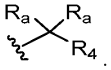
60. The compound of claim 57 or 59, wherein each occurrence of R_b is independently H or (C_1-C_6)alkyl.

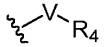
61. The compound of any one of claims 57 and 59-60, wherein each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

62. The compound of any one of claims 1 and 56-59, wherein each occurrence of R_2 is independently H, CH_3, OH, NH_2, or halogen.

63. The compound of claim 1, wherein the structural moiety  has the structure of  .

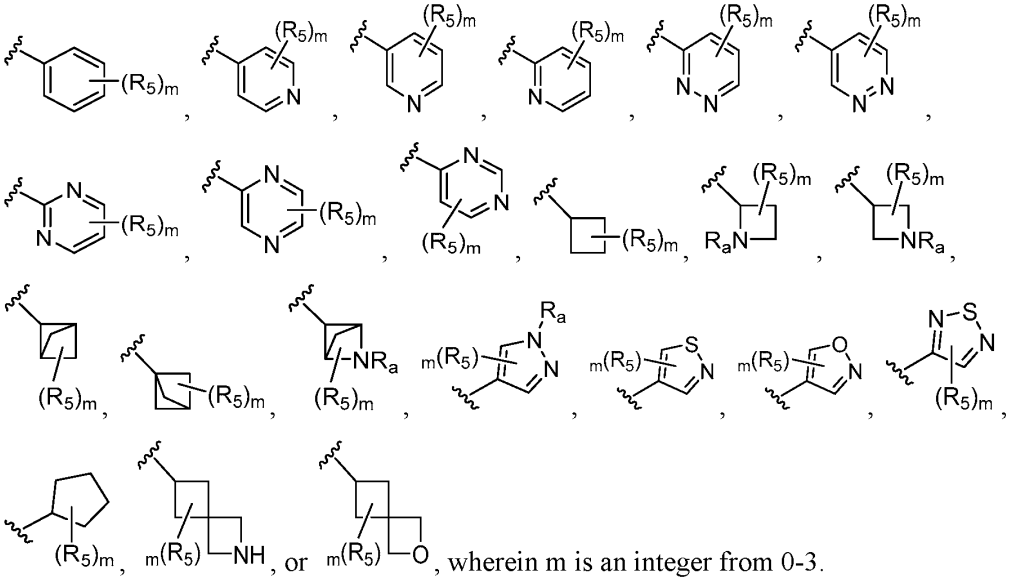
64. The compound of claim 1, wherein the structural moiety  has the structure of  .

65. The compound of claim 1, wherein the structural moiety  has the structure of  .

66. The compound of claim 1, wherein the V and R_4 of the structural moiety  taken together form a (C_4-C_{10})heterospiroalkyl.

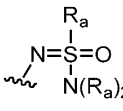
67. The compound of claim 1, wherein V is absent.

68. The compound of any one of claims 1 and 63-67, wherein R_4 is (C_1-C_6)alkyl,

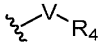


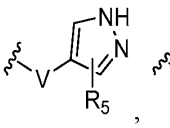
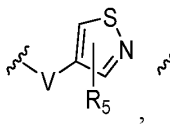
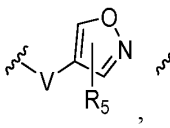
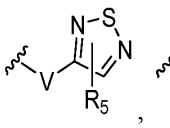
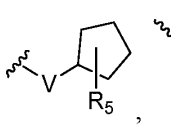
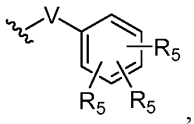
wherein m is an integer from 0-3.

69. The compound of claim 1 or 68, wherein each occurrence of R_5 is independently H, (C_1-C_6)alkyl, halogen, OR_a, OH, NH_2, $N(R_a)COR_a$, CN, CF_3, (C_1-C_6)haloalkyl, or

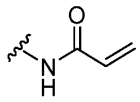


and each occurrence of R_a is independently H, (C_2-C_6)alkenyl, or (C_1-C_6)alkyl.

70. The compound of any one of claims 1, 63-66, and 68-69, wherein the structural moiety  has the structure of

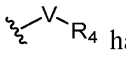
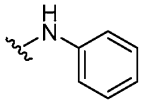
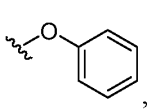
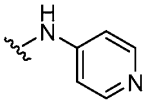
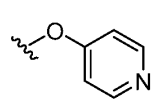
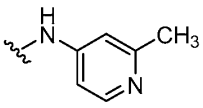
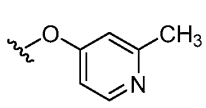
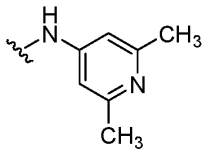
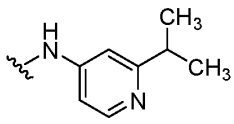
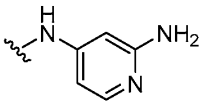
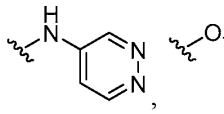
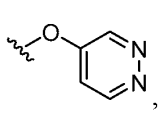
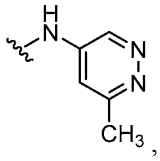
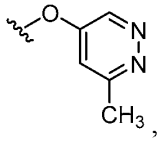
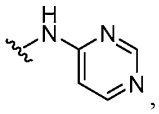
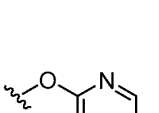
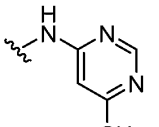
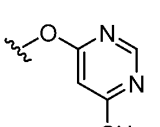
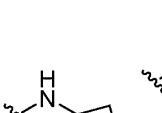
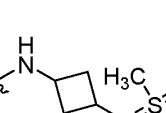
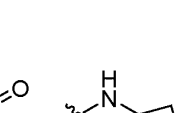
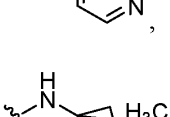
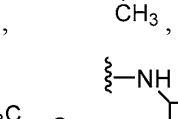
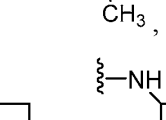






, or

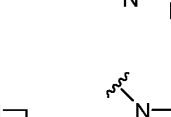
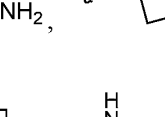
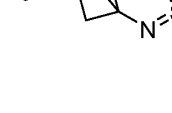
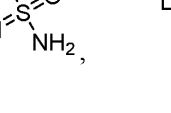
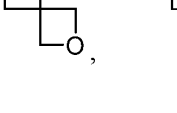
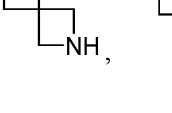
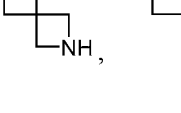
, wherein V is $C(R_a)_2$, O, NR_a, $N(C=O)R_a$, or NSO_2R_a and V' is CR_a or N.

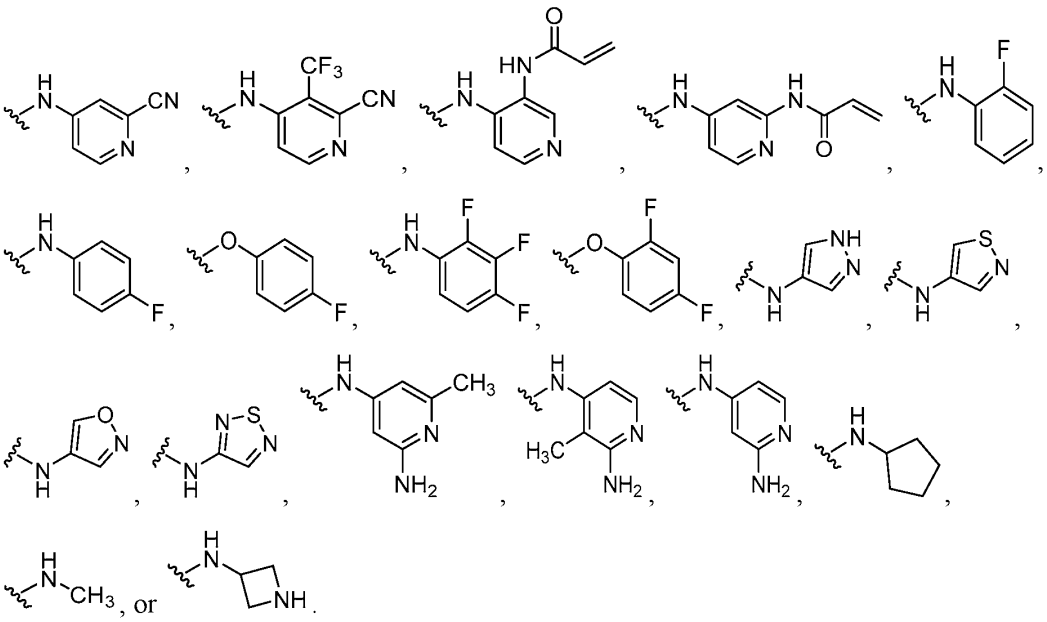
71. The compound of claim 1 or 70, wherein each occurrence of R_5 is independently H, CH_3, halogen, OH, CN,  , CF_3, $(C_1\text{-}C_6)$haloalkyl, or NH_2.

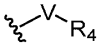
72. The compound of any one of claims 1, 19-20, 21, 51, and 69, wherein each occurrence of R_a is independently H, $(C_2\text{-}C_6)$alkenyl, or $(C_1\text{-}C_6)$alkyl.

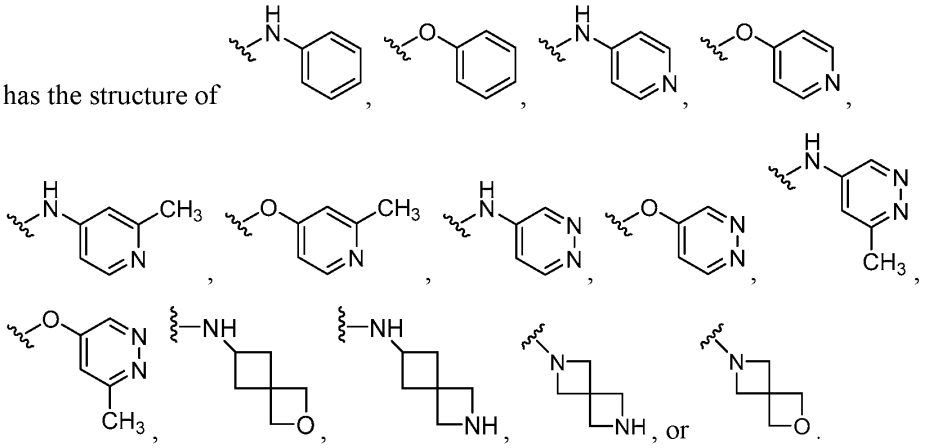
73. The compound of any one of claims 1, 19-20, 21, 51, 69, and 72, wherein each occurrence of R_a is H, CH_3, or CH_2CH_3.

74. The compound of any one of claims 1, 63-66, and 68-73, wherein the structural moiety  has the structure of
























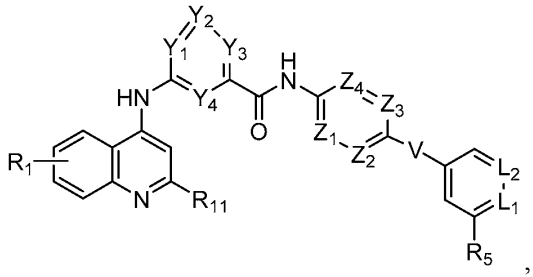








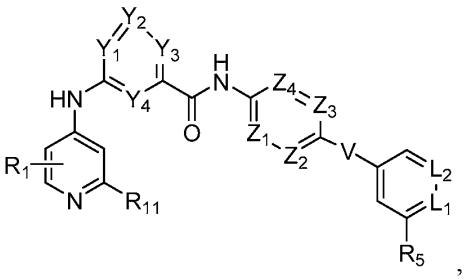


75. The compound of claim 1, 63-66, and 68-74, wherein the structural moiety  has the structure of



76. The compound of claim 1 or 32, wherein the compound of Formula Ia has the structure of

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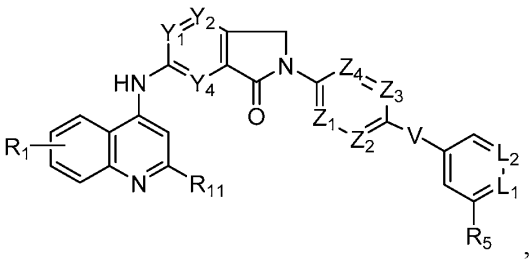
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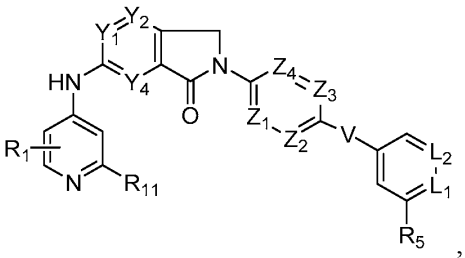
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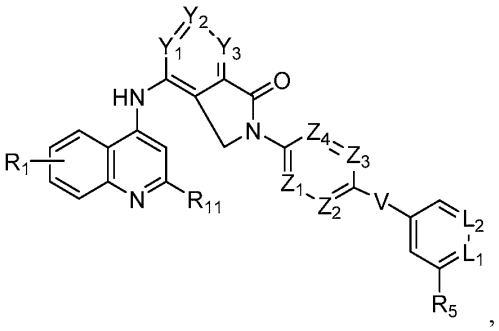
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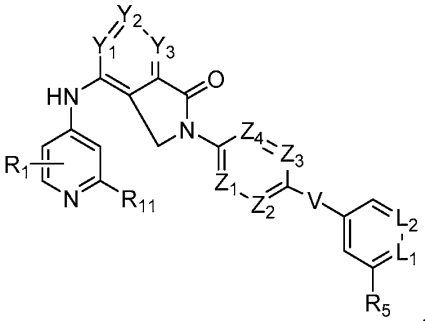
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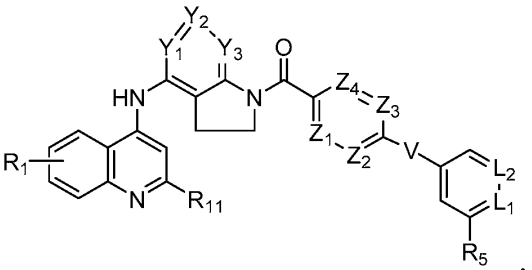
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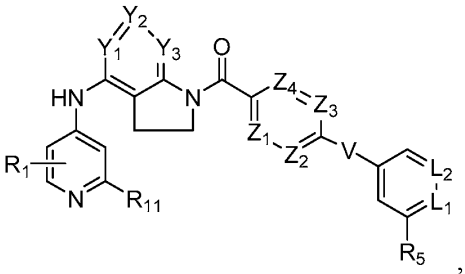
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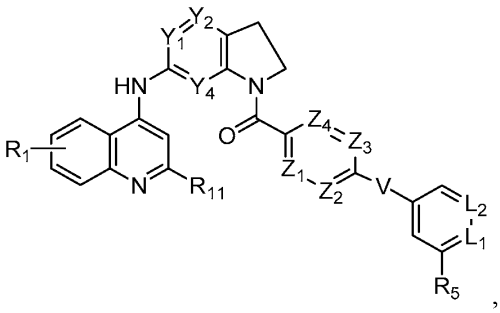
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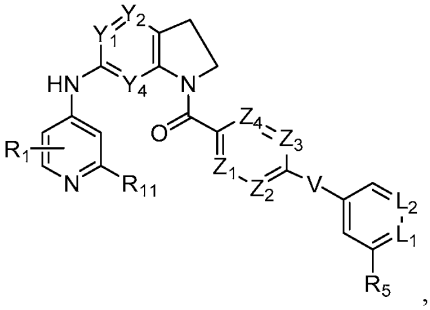
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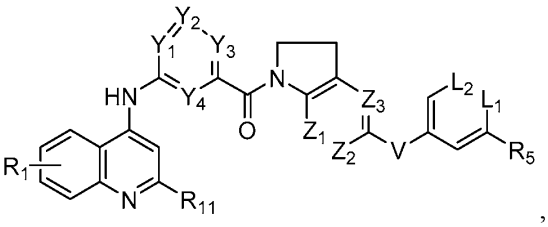
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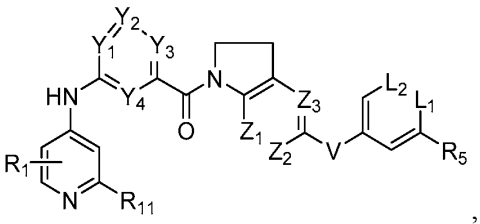
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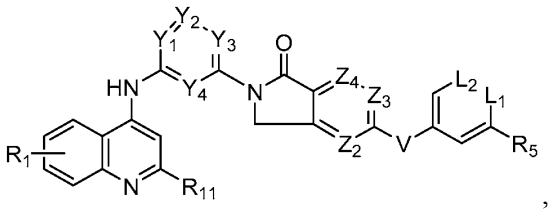
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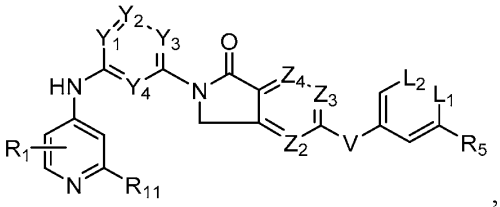
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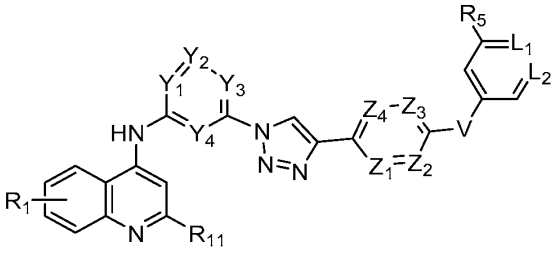
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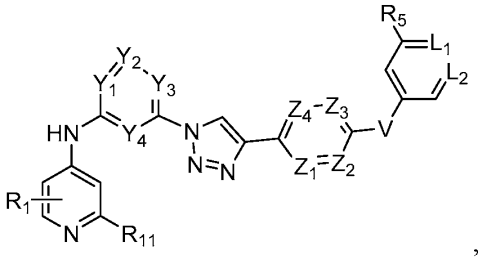
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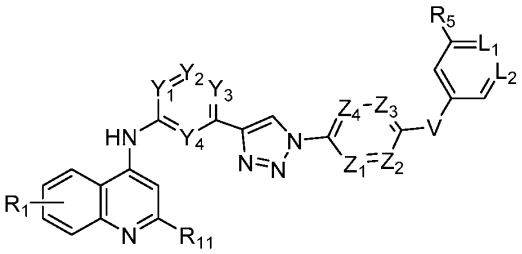
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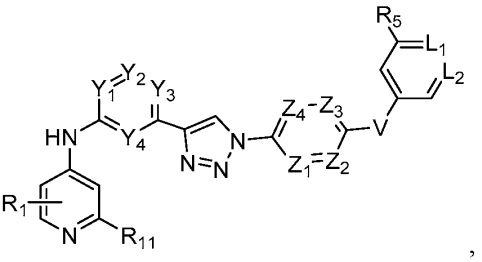
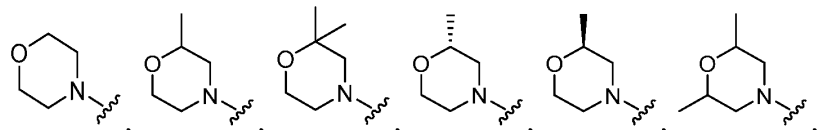
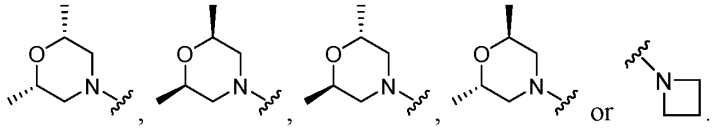

,

wherein R_1 is H, (C_1-C_6)alkyl, $N(R_a)_2$, (C_3-C_7)heterocycloalkyl, or halogen; R_5 and R_{11} are each independently H or CH_3; Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, Z_3, Z_4, L_1, and L_2 are each independently CH or N; and V is NH or O.

77. The compound of claim 76, wherein R_1 is H, F, Cl, Br, CH_3, CH_2CH_3, $CH(CH_3)_2$, NH_2, NMe_2,


or

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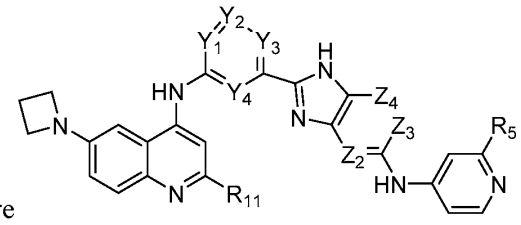
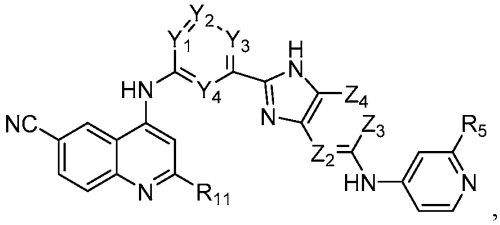
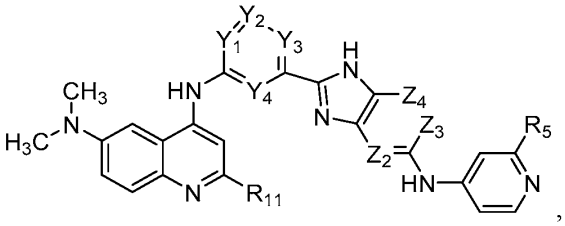
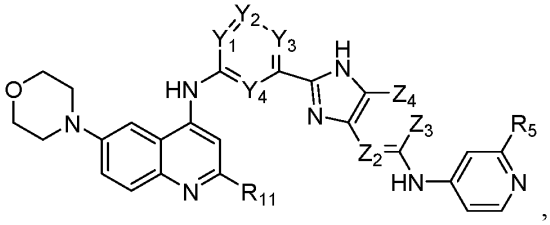
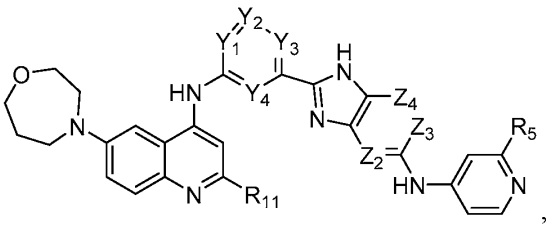
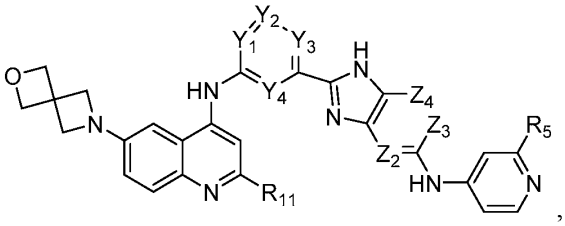
78. The compound of claim 1 or 50, wherein the compound of Formula Ib has the structure  ,

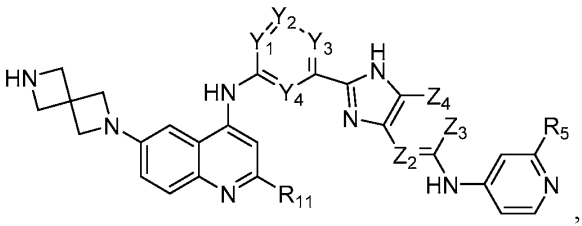
 ,

 ,

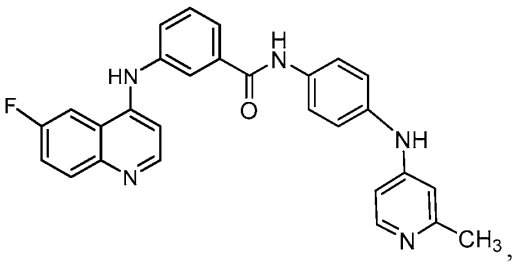
 ,

 ,

 , or


, wherein R_{11} and R_5 are each independently H or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N.

79. The compound of claim 1, wherein the compound of Formula Ia is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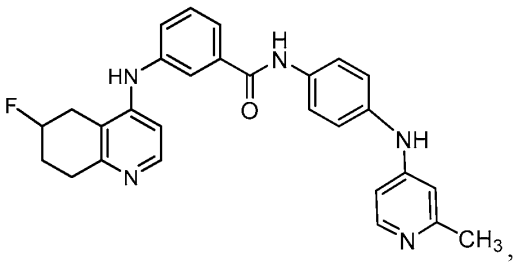
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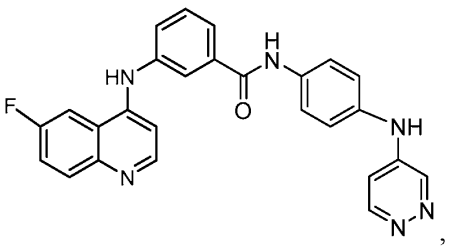
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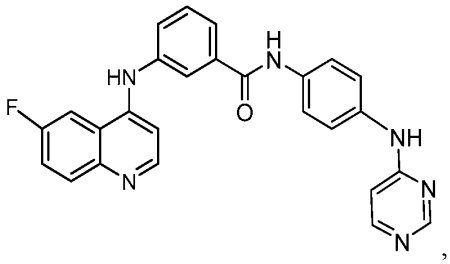
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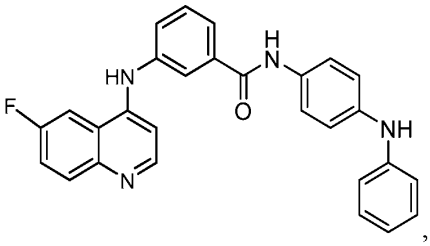
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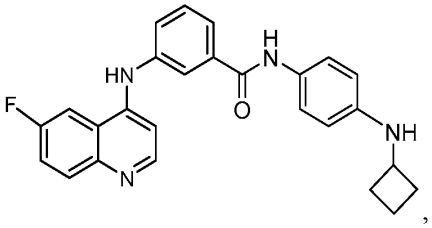
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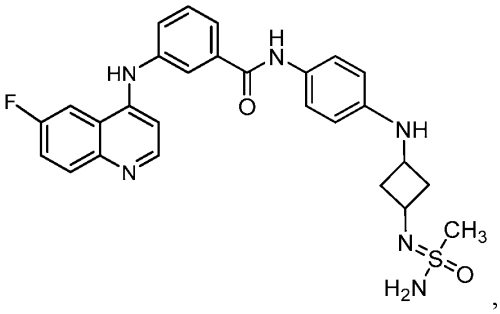
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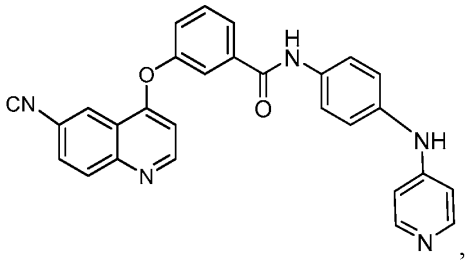
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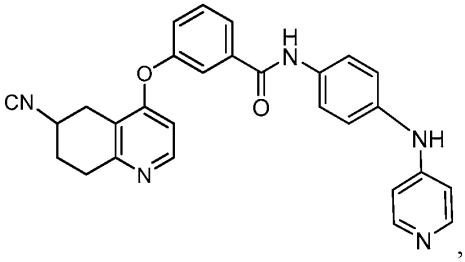
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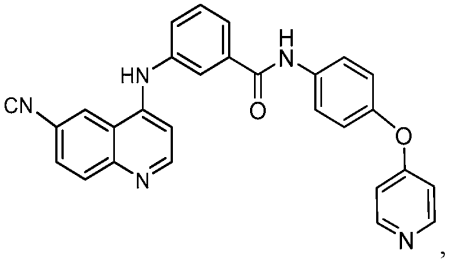
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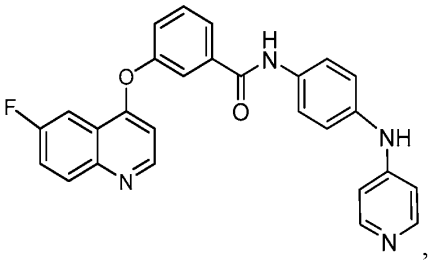
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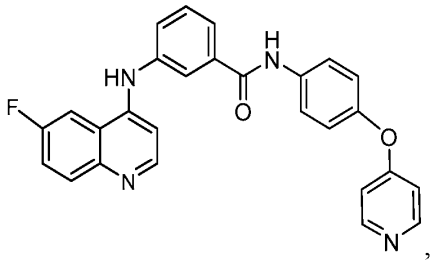
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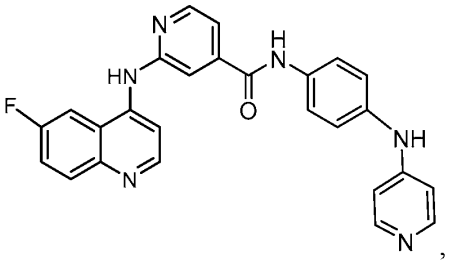
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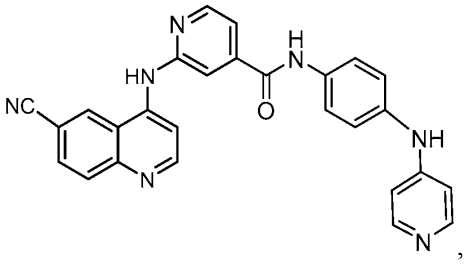
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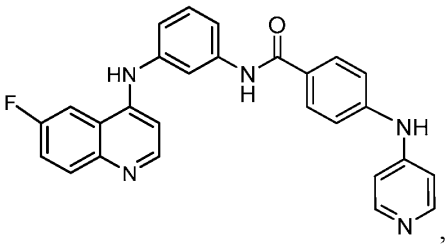
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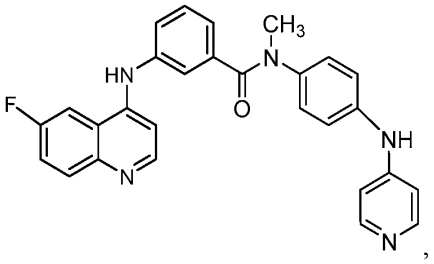
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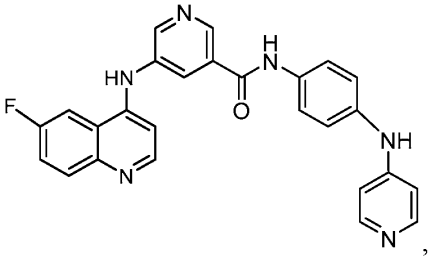
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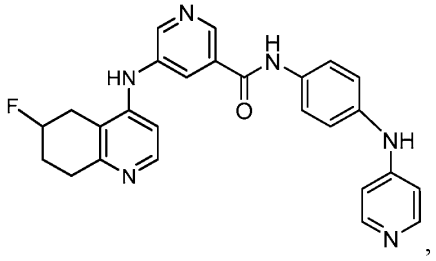
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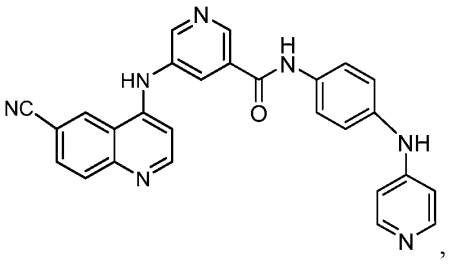
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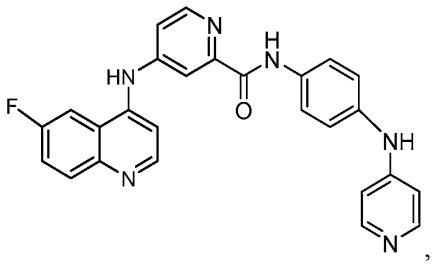
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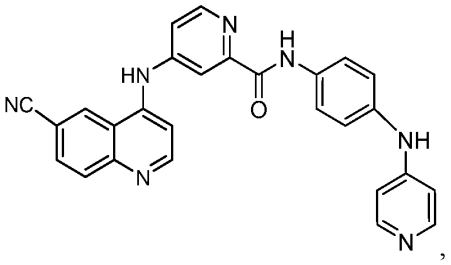
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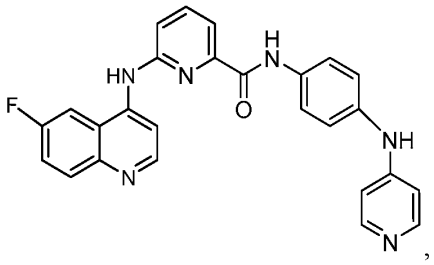
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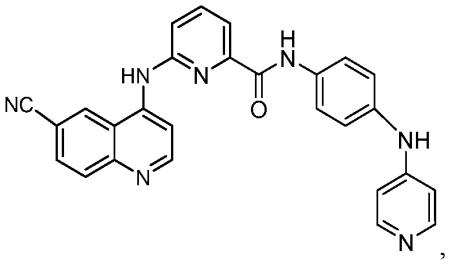
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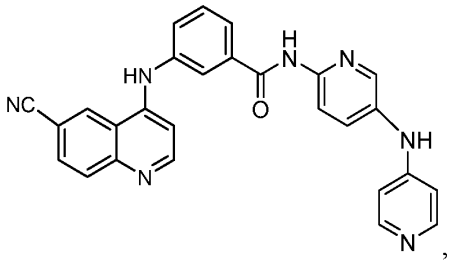
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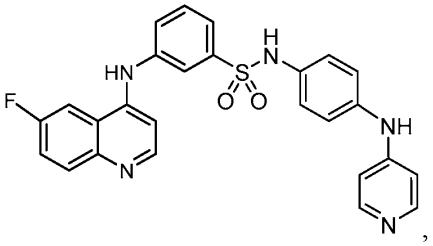
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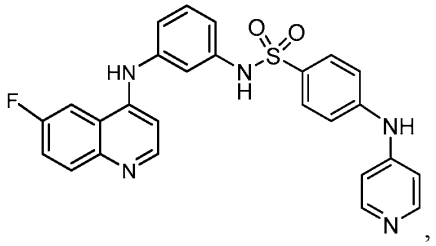
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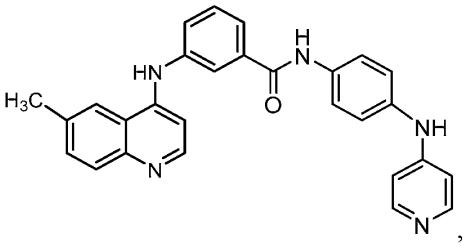
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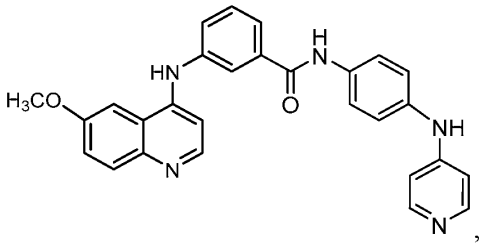
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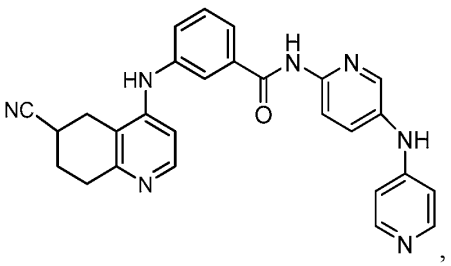
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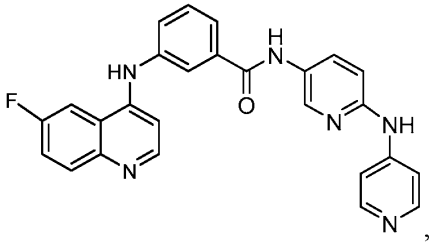
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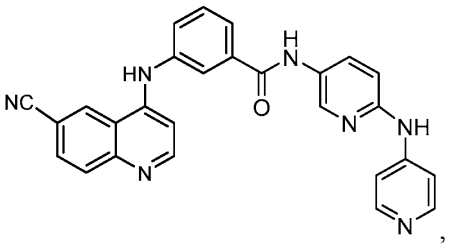

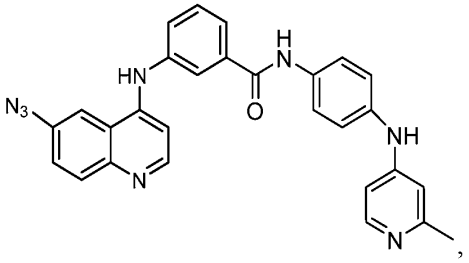

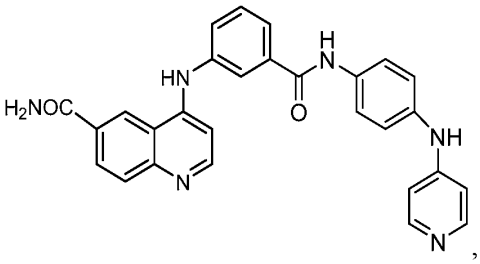

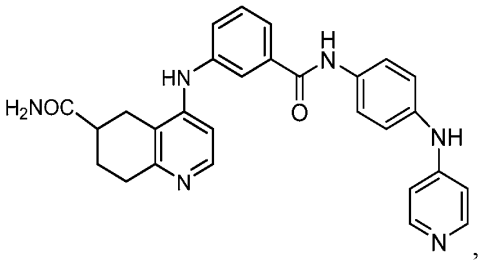

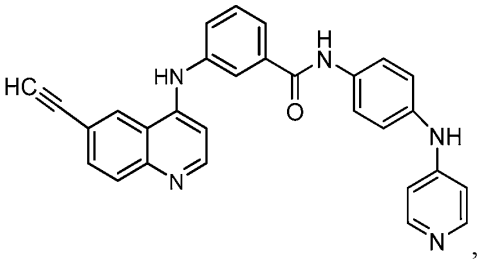

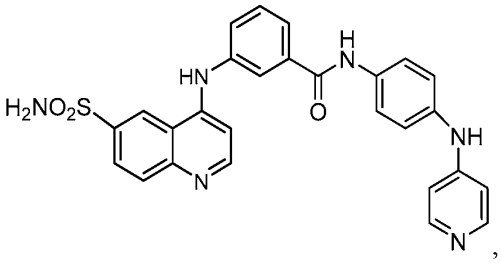

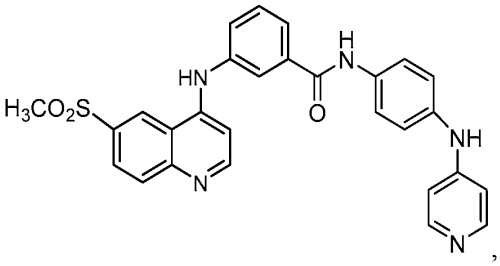

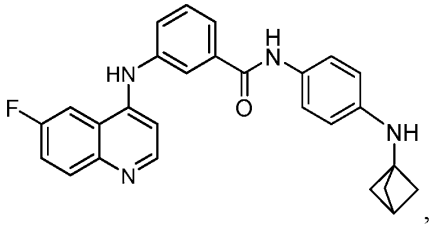

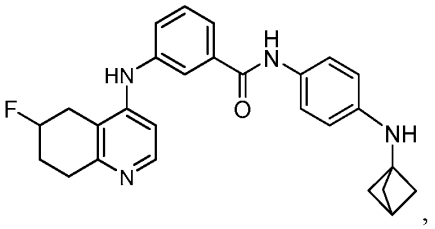

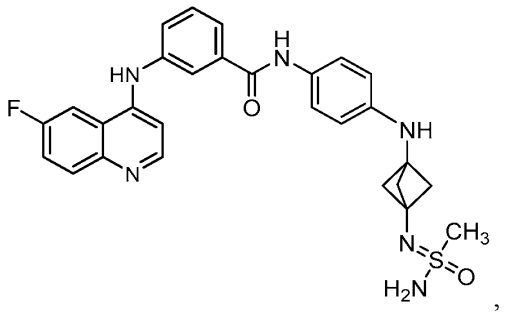

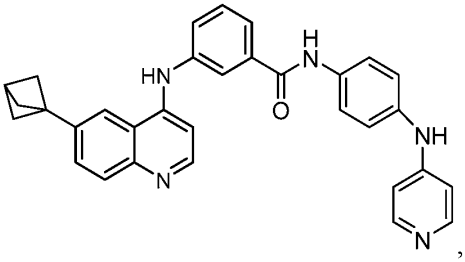
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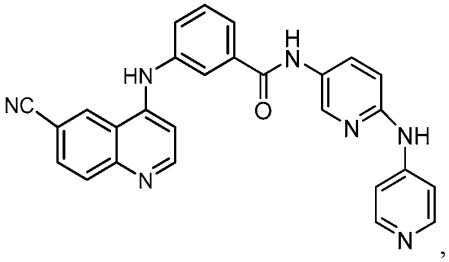
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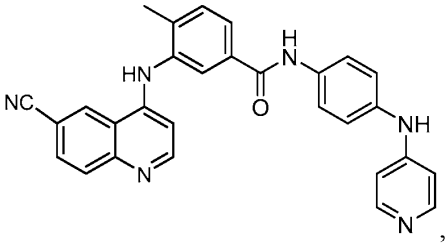
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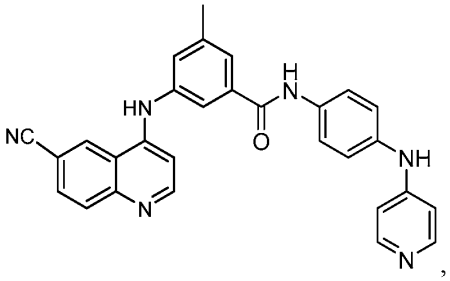
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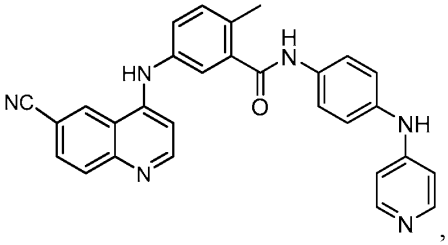
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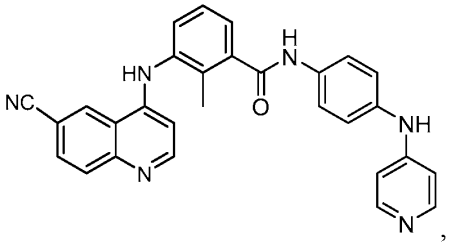
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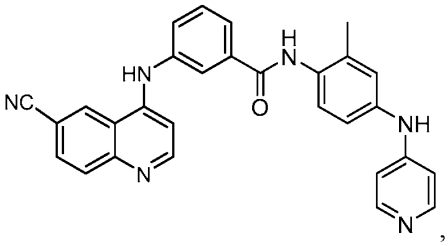
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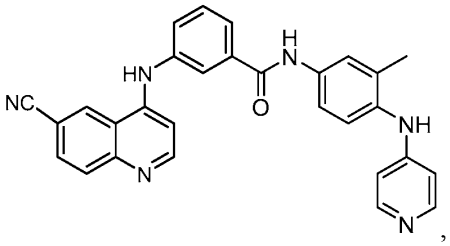
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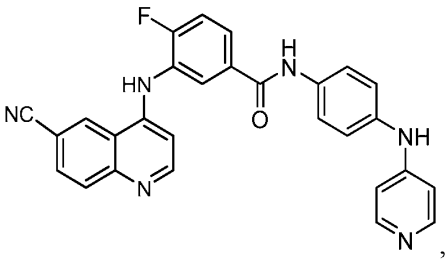
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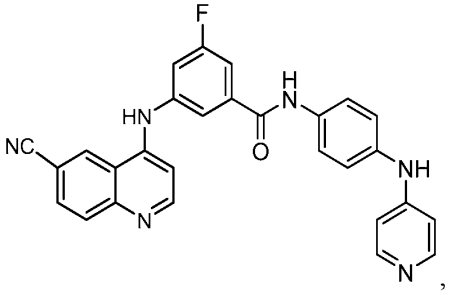
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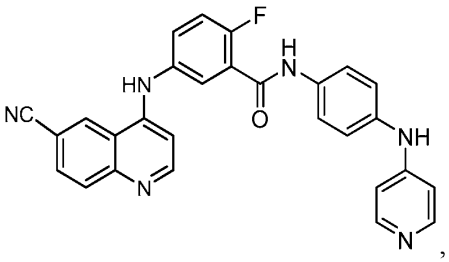
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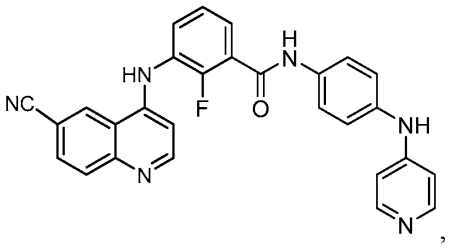
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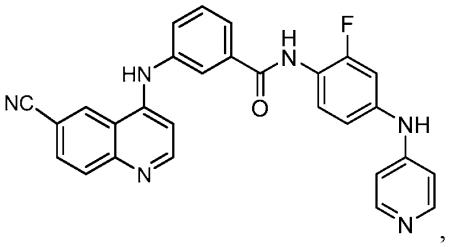
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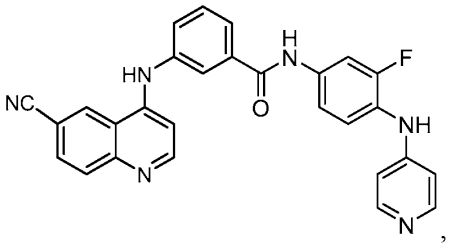
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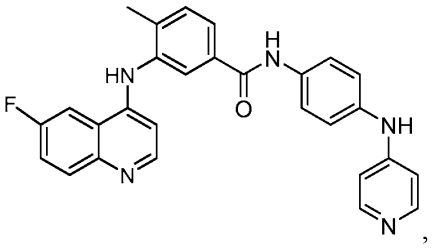
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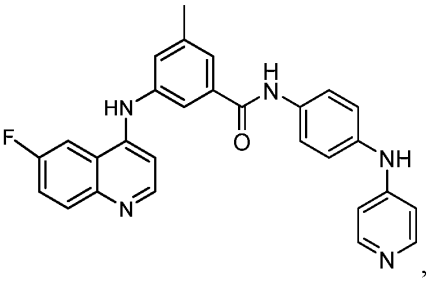
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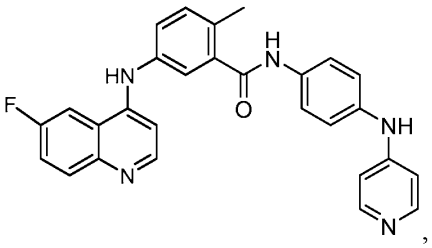
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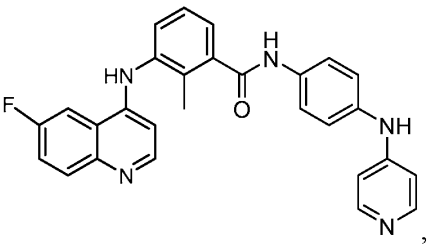
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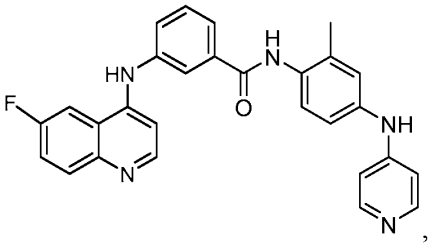
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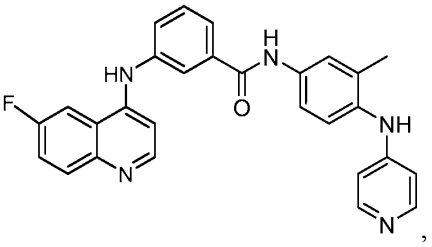
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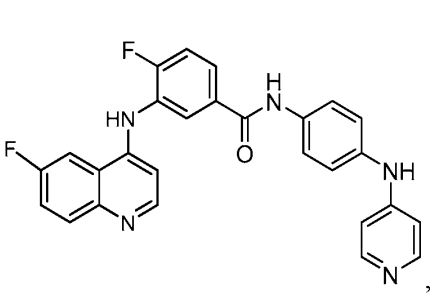
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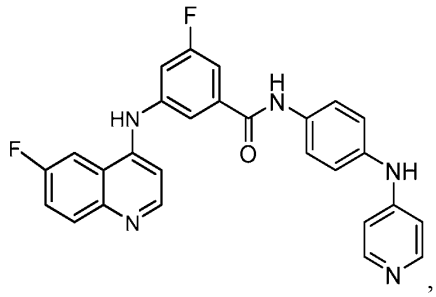
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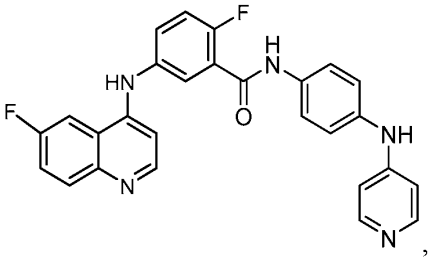
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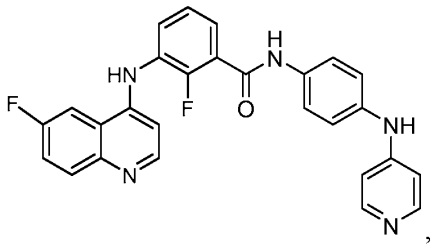
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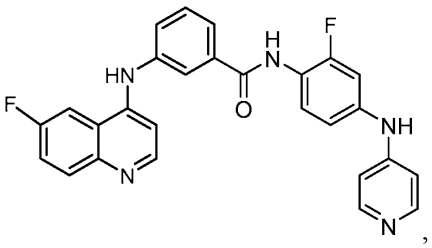
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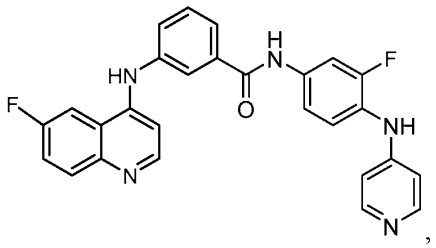
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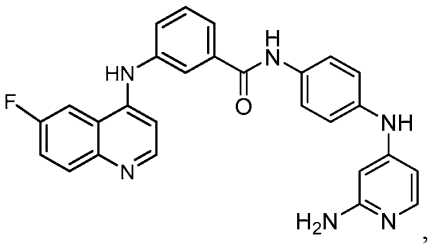
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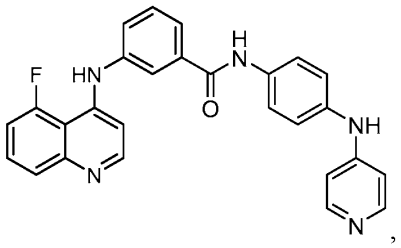
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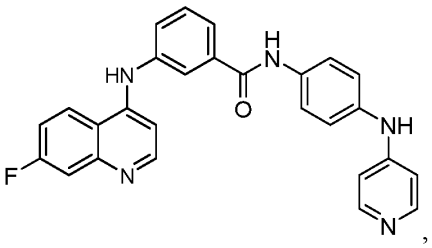
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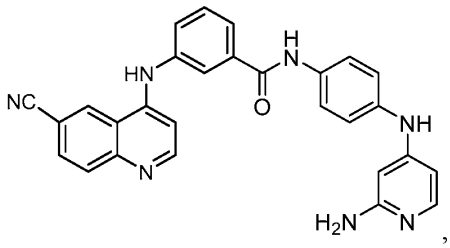
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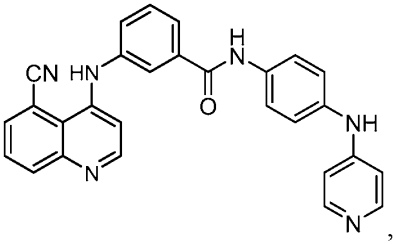
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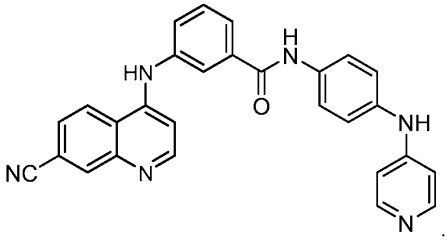
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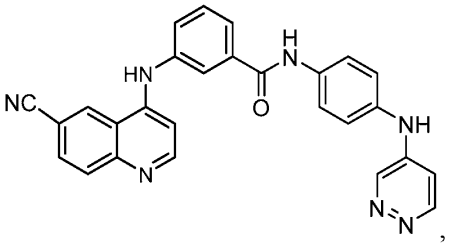
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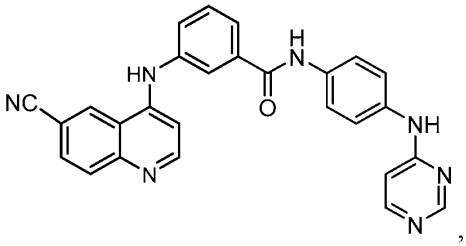
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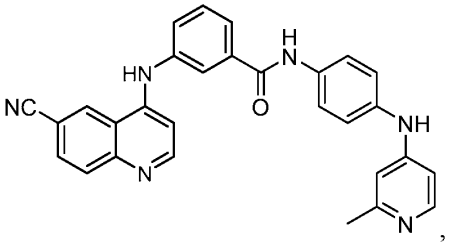
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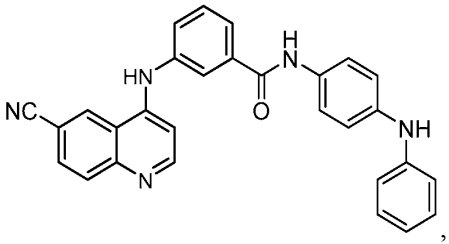
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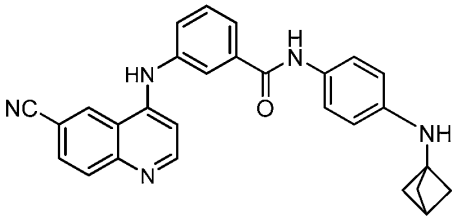
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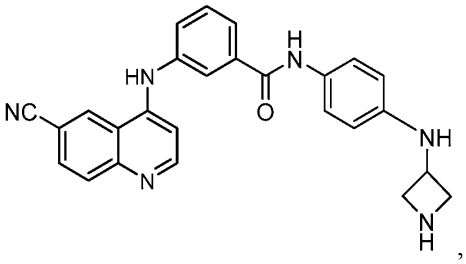
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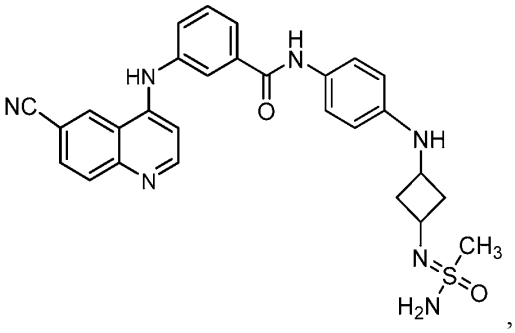
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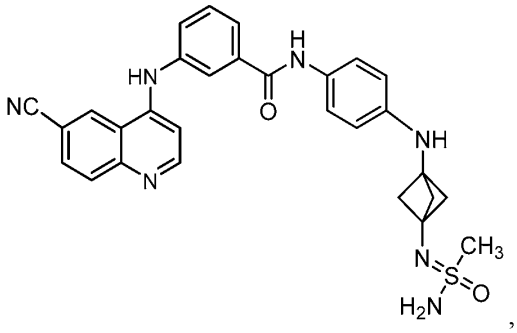
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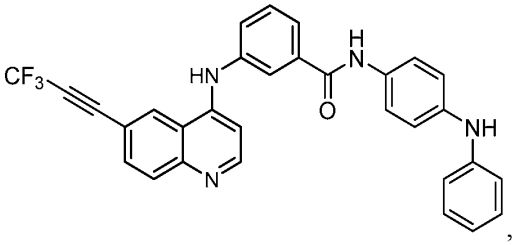

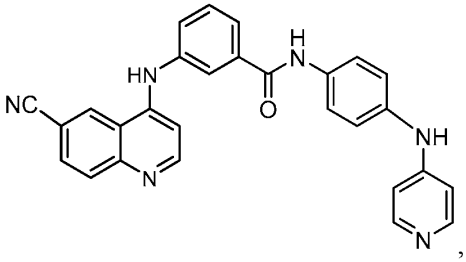

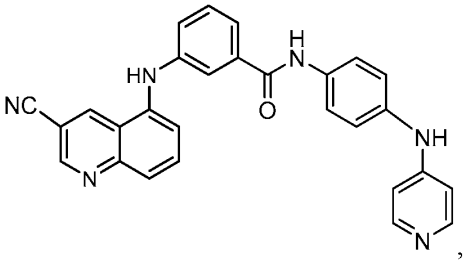

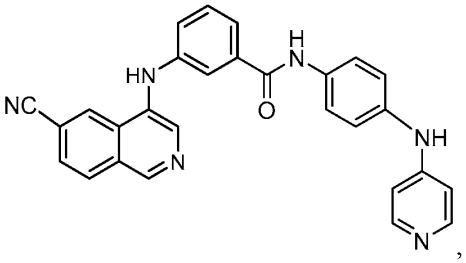

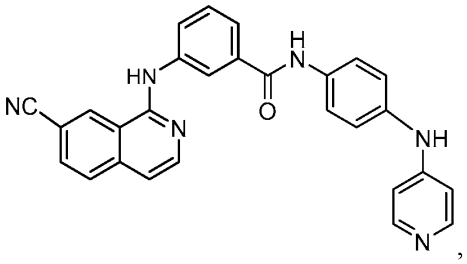

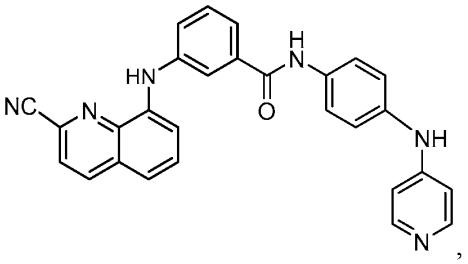

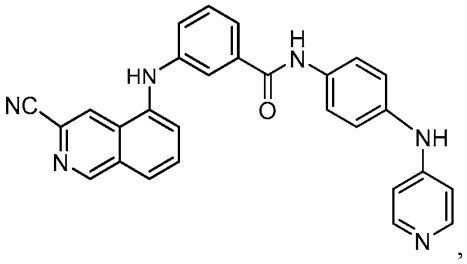

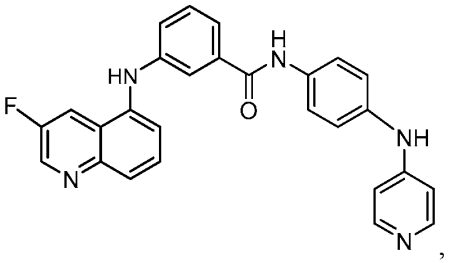

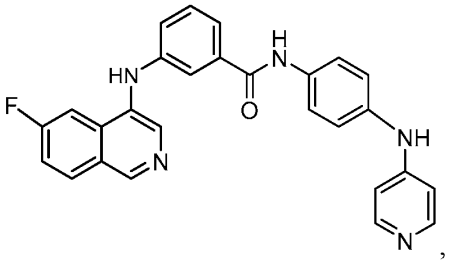

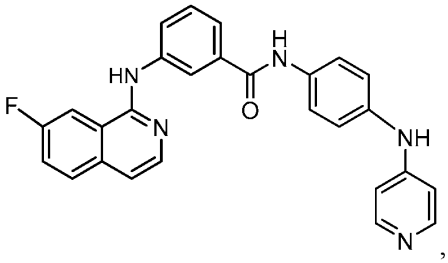

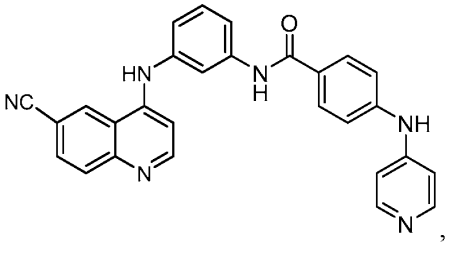

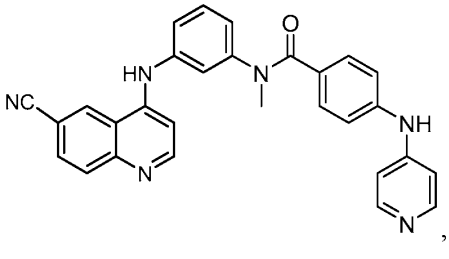

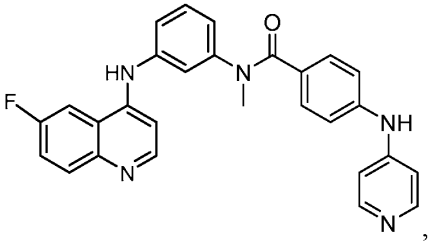
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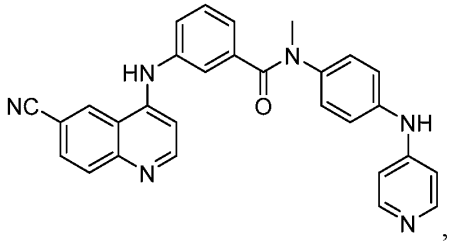
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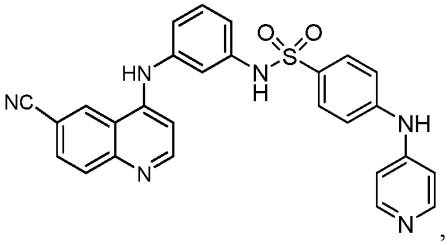
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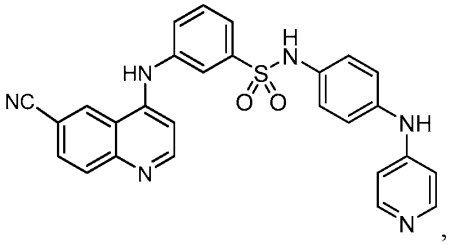
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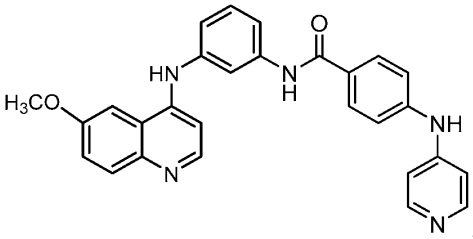
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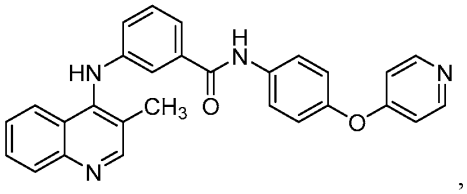
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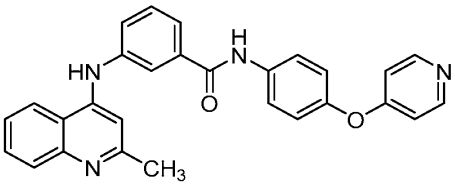
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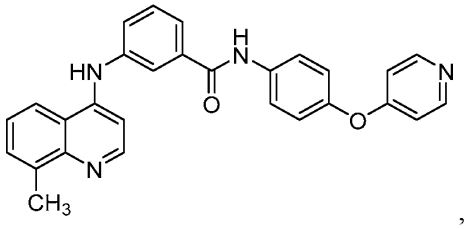
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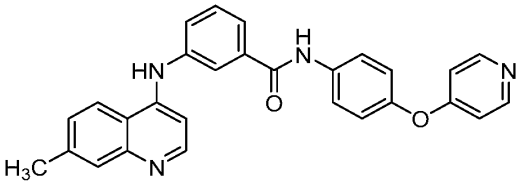
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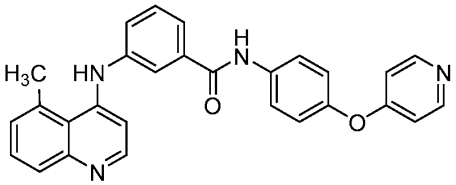
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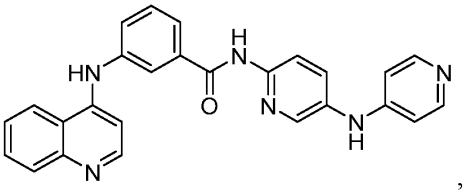
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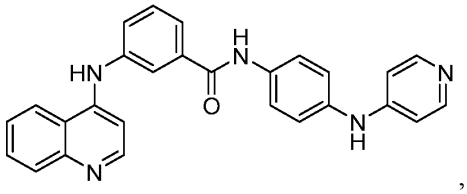
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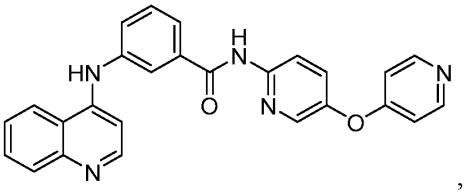
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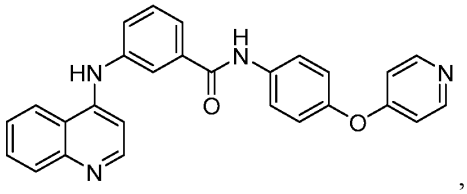
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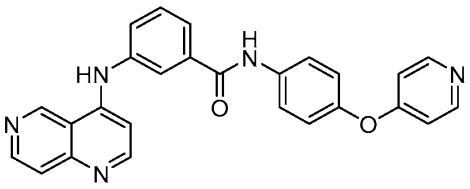
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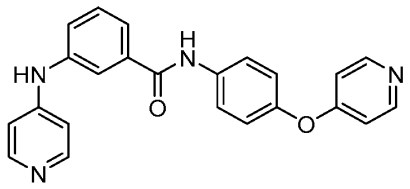
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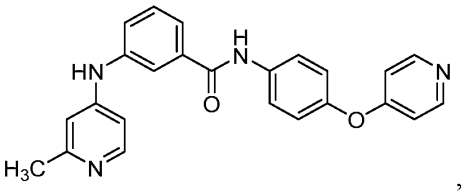
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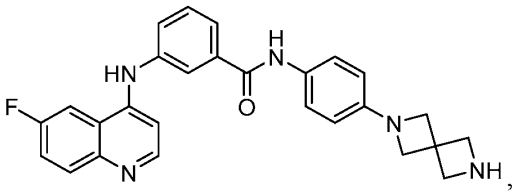
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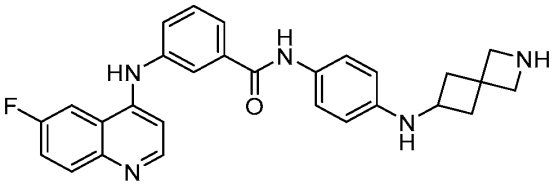
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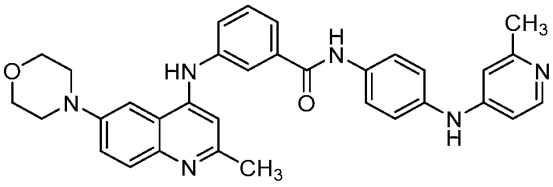
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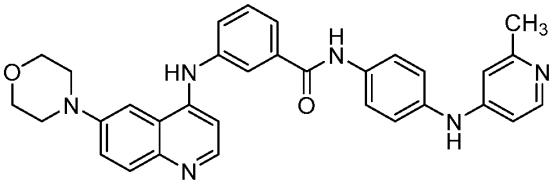
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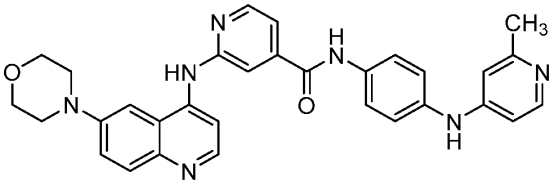
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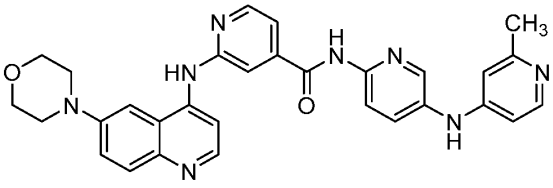
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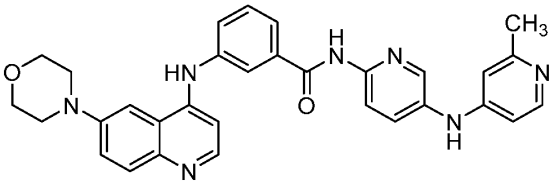
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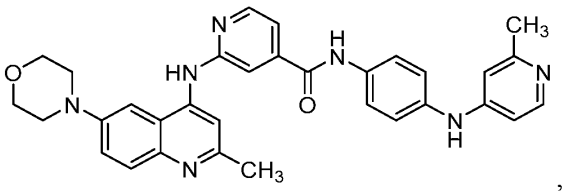
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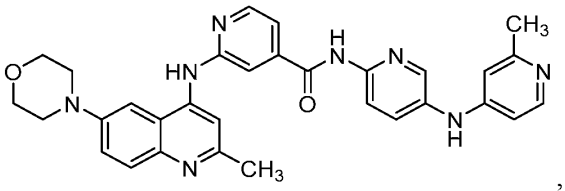
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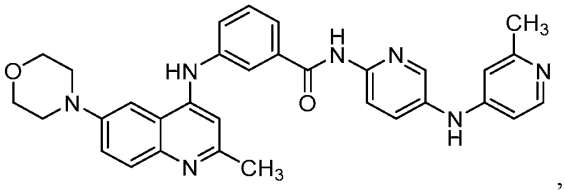
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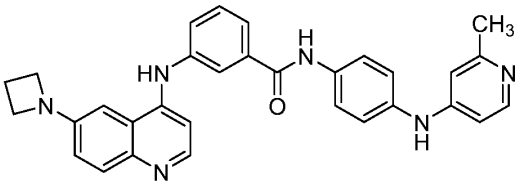
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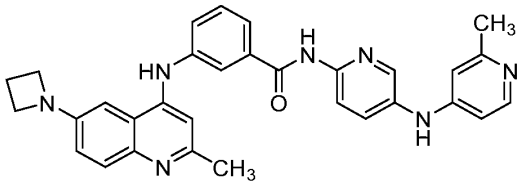
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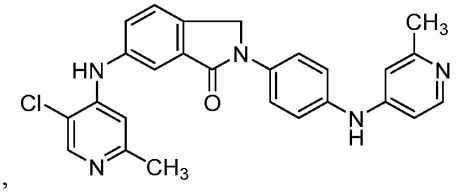
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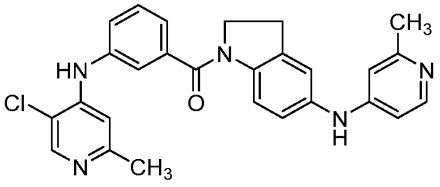
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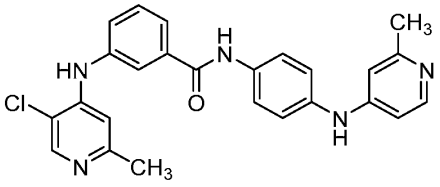
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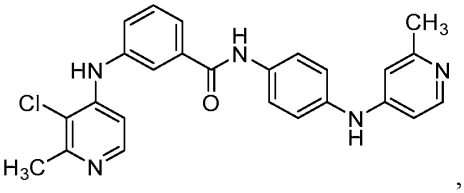
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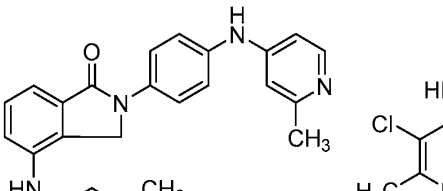
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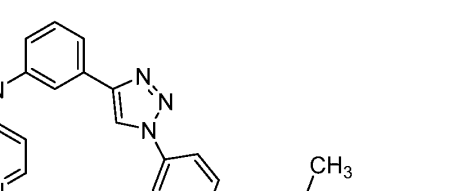
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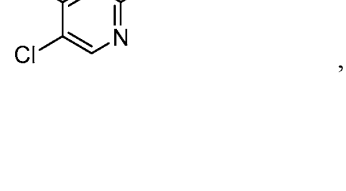
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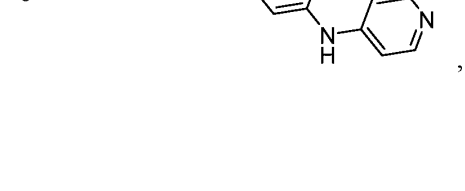
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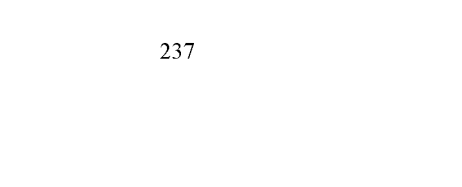
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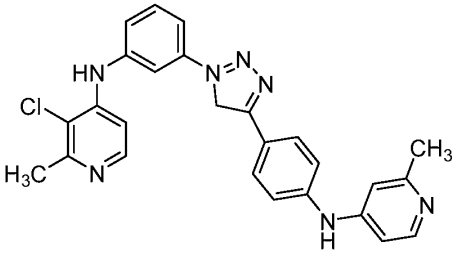
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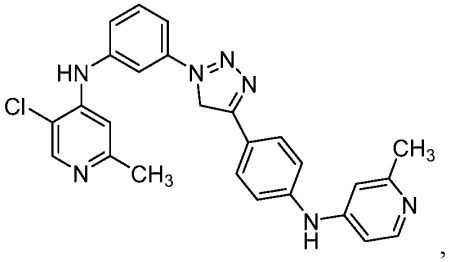
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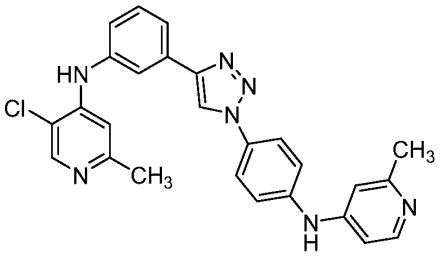
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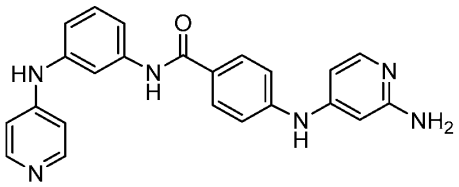
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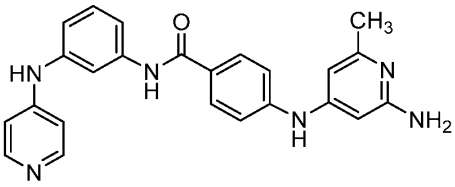
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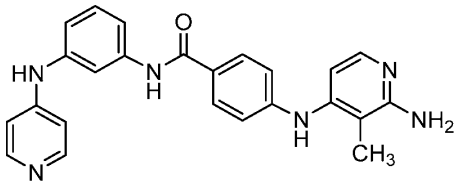
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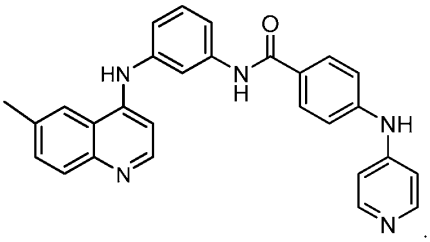
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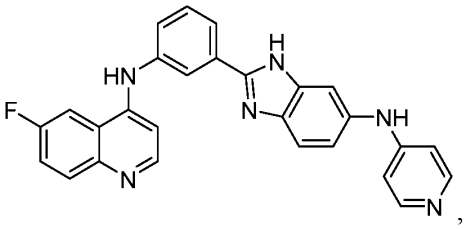
80. The compound of claim 1, wherein the compound of Formula Ib is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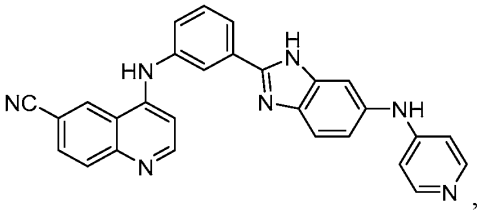
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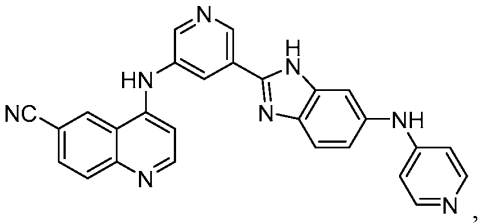
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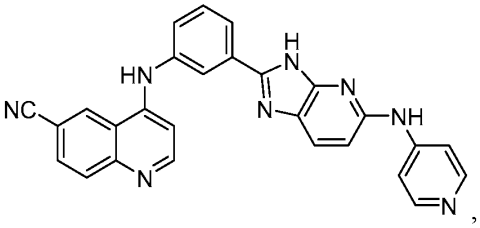
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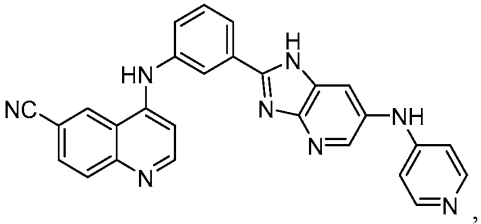
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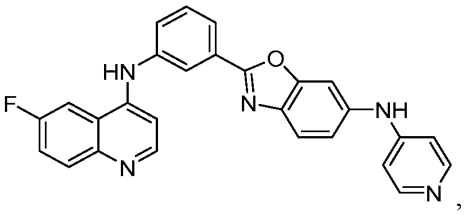
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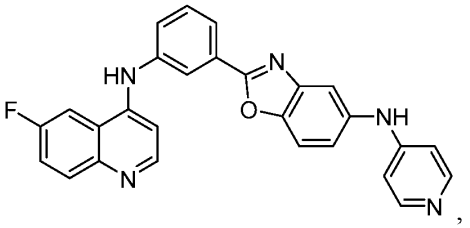
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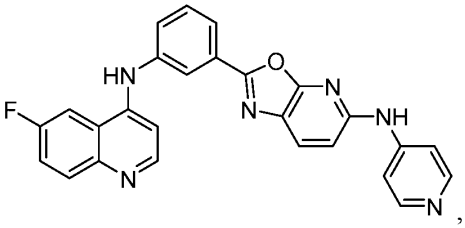
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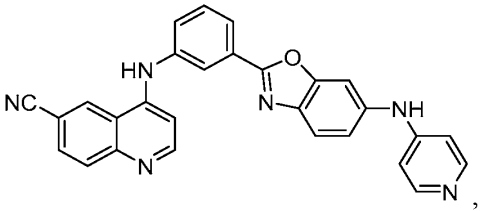
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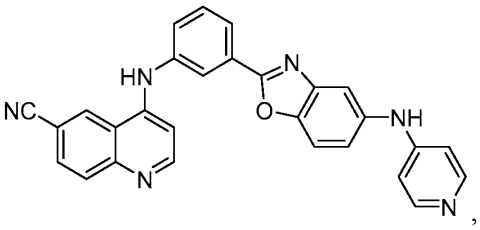
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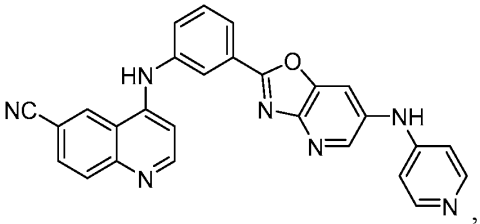
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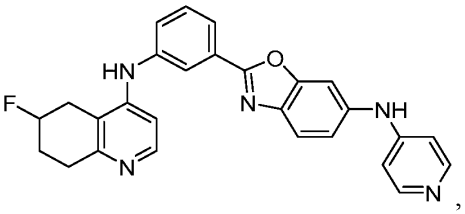
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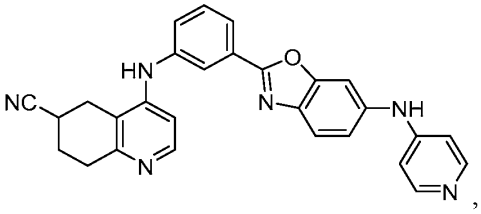
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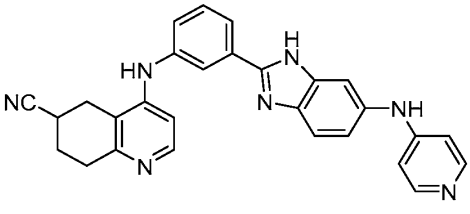
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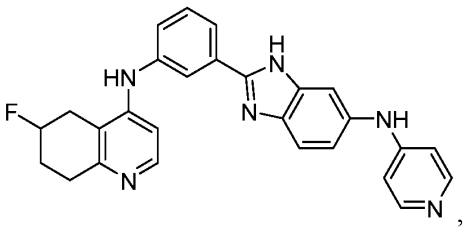
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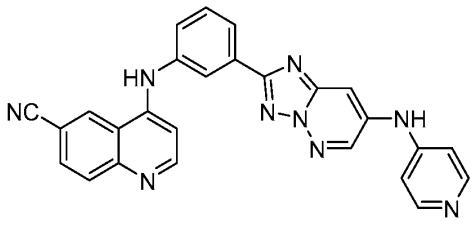
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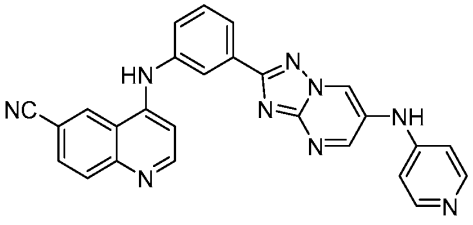
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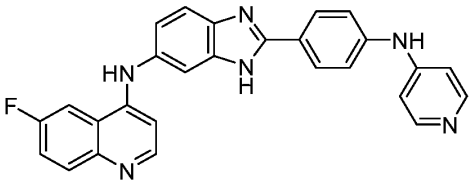
81. The compound of claim 1, wherein the compound of Formula Ic is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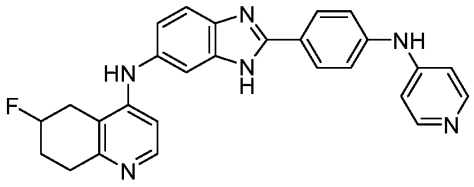
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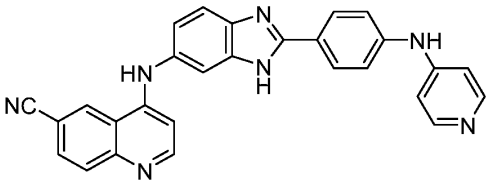
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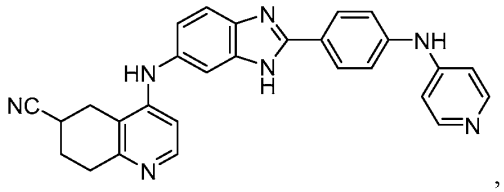
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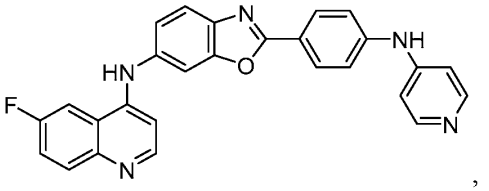
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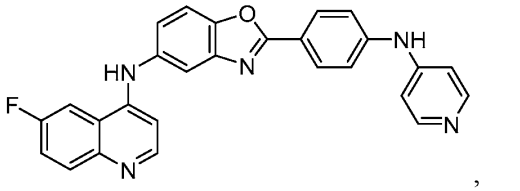
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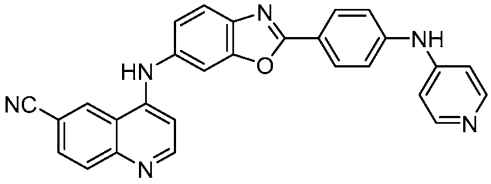
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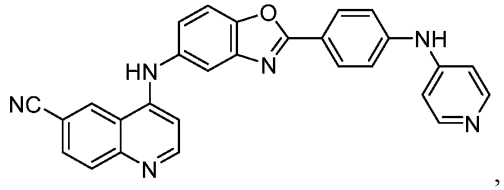
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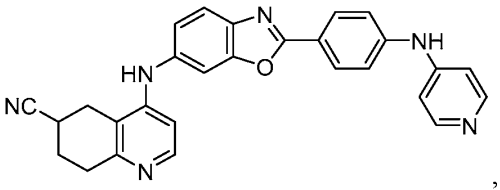
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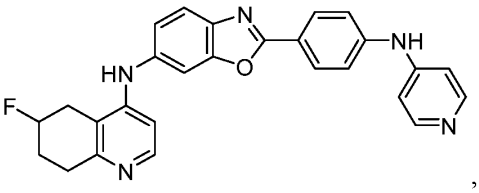
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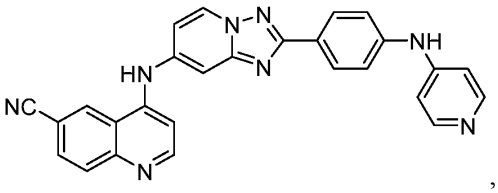
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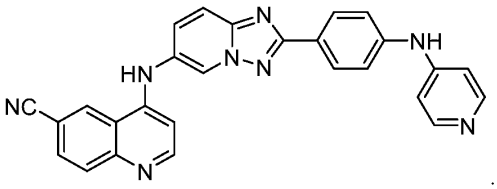
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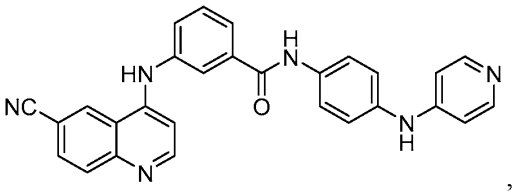
82. The compound of claim 1, wherein the compound is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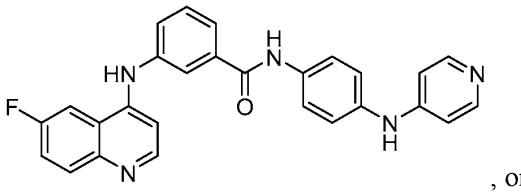
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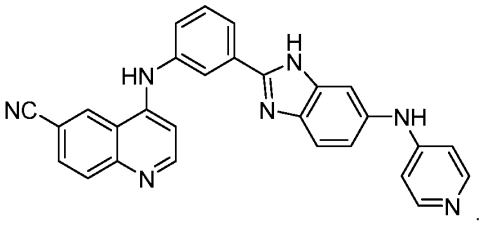
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83. The compound of claim 1, wherein the compound is selected from the group consisting of compounds 2-22 in Examples 2-22, respectively.

84. A method of treating a disease in a subject in need thereof comprising administering to the subject an effective amount of the compound of any one of the preceding claims.

85. The method of claim 84, wherein the disease is selected from the group consisting of neurodegenerative disease, cachexia, anorexia, obesity, obesity's complication, inflammatory disease, viral-induced inflammatory reaction, Gulf War Syndrome, tuberous sclerosis, retinitis pigmentosa, transplant rejection, cancer, an autoimmune disease, ischemic tissue injury, traumatic tissue injury and a combination thereof.

86. The method of claim 85, wherein the disease is neurodegenerative disease.

87. The method of claim 86, wherein the neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Motor Neuron Disease, Huntington's disease, HIV-induced neurodegeneration, Lewy Body Disease, spinal muscular atrophy, prion disease, spinocerebellar ataxia, familial amyloid polyneuropathy, multiple sclerosis, and a combination thereof.

88. The method of claim 85, wherein the disease is cachexia or anorexia.

89. The method of claim 85, wherein the disease is obesity or obesity's complication.

90. The method of claim 89, wherein the obesity's complication is selected from the group consisting of glucose intolerance, hepatic steatosis, dyslipidemia, and a combination thereof.

91. The method of claim 85, wherein the disease is inflammatory disease.

92. The method of claim 91, wherein the inflammatory disease is selected from the group consisting of atopic dermatitis, allergy, asthma, and a combination thereof.

93. The method of claim 85, wherein the disease is viral-induced inflammatory reaction.

94. The method of claim 93, wherein the viral-induced inflammatory reaction is SARS-induced inflammatory pneumonitis, coronavirus disease 2019, or a combination thereof.

95. The method of claim 85, wherein the disease is Gulf War Syndrome or tuberous sclerosis.

96. The method of claim 85, wherein the disease is retinitis pigmentosa or transplant rejection.

97. The method of claim 85, wherein the disease is ischemic tissue injury or traumatic tissue injury.

98. The method of claim 85, wherein the disease is cancer.

99. The method of claim 98, wherein the cancer is selected from the group consisting of adult T-cell leukemia/lymphoma, bladder, brain, breast, cervical, colorectal, esophageal, kidney, liver, lung, nasopharyngeal, pancreatic, prostate, skin, stomach, uterine, ovarian, and testicular cancer.

100. The method of claim 98, wherein the cancer is leukemia.

101. The method of claim 100, wherein the leukemia is adult T-cell leukemia/lymphoma.

102. The method of claim 101, wherein the adult T-cell leukemia/lymphoma is caused by human T-cell lymphotropic virus.

103. The method of claim 85, wherein the disease is autoimmune disease.

104. The method of claim 103, wherein the autoimmune disease is selected from the group consisting of achalasia, Addison's disease, adult Still's disease, agammaglobulinemia, alopecia areata, amyloidosis, ankylosing spondylitis, anti-glomerular basement membrane disease, anti-tubular basement membrane antibody nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease, autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal and neuronal neuropathy, Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, chronic recurrent multifocal osteomyelitis, Churg-Strauss syndrome, eosinophilic granulomatosis, cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis, eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura, pemphigoid gestationis, hidradenitis suppurativa (acne inversa), hypogammalglobulinemia, IgA nephropathy, IgG4-related sclerosing disease, immune thrombocytopenic purpura, inclusion body myositis, interstitial cystitis, juvenile arthritis, juvenile diabetes (type 1 diabetes), juvenile myositis, Kawasaki disease, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease, lupus, chronic Lyme disease, Meniere's disease, microscopic polyangiitis, mixed connective tissue disease, Mooren's ulcer, Mucha-Habermann disease, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis,

myositis, narcolepsy, neonatal lupus, neuromyelitis optica, neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, pediatric autoimmune neuropsychiatric disorder, paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria, Parry Romberg syndrome, pars planitis (peripheral uveitis), Parsonage-Turner syndrome, pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syndrome, polyarteritis nodosa, polyglandular syndrome type I, polyglandular syndrome type II, polyglandular syndrome type III, polymyalgia rheumatica, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia, pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, relapsing polychondritis, restless legs syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm and testicular autoimmunity, stiff person syndrome, subacute bacterial endocarditis, Susac's syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis (giant cell arteritis), thrombocytopenic purpura, Tolosa-Hunt syndrome, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, uveitis, vasculitis, vitiligo, Vogt-Koyanagi-Harada disease, and a combination thereof.

105. The method of any one of claims 85-104, wherein the compound modulates Akt3 in immune cells.

106. The method of claim 105, wherein the immune cells are selected from the group consisting of T cells, B cells, macrophages, and glial cells.

107. The method of claim 106, wherein the glial cells are astrocytes, microglia, or oligodendrocytes.

108. The method of claim 106, wherein the T cells are T regulatory cells.

109. The method of claim 84 or 85, wherein the compound activates Akt3 signaling.

110. The method of claim 84 or 85, wherein the compound inhibits Akt3 signaling.

111. The method of claim 84 or 85, wherein the compound increases T regulatory cell activity or production.

112. The method of claim 84 or 85, wherein the compound decreases T regulatory cell activity or production.

113. The method of any one of claims 84-112, further comprising administering a second therapeutic agent to the subject.

114. The method of claim 113, wherein the second therapeutic agent is selected from the group consisting of a nutrient supplementation, a chemotherapeutic, an anti-inflammatory, an immunosuppressant, a cholinesterase inhibitor, an antidepressant, an anxiolytic, an antipsychotic, riluzole, edavarone, a dopamine agonist, a MAO B inhibitor, a catechol O-methyltransferase inhibitor, an anticholinergic, an anticonvulsant, tetrabenazine, carbidopa-levodopa, an antispastic, an antibody, a fusion protein, an enzyme, a nucleic acid, a ribonucleic acid, an anti-proliferative, a cytotoxic agent, an appetite stimulant, a 5-HT3 antagonist, a Cox-2 inhibitor, and a combination thereof.

115. The method of any one of claims 84-112, wherein the method further comprises treating the subject with an immune therapeutic agent, an immune modulator, an costimulatory activating agonist, a cytokine, a chemokine, a chemokine factor, an oncolytic virus, a biologics, a vaccine, a small molecule, a targeted therapy, an anti-inflammatory agent, a cell therapy, a chemotherapeutic agent, or radiation therapy.