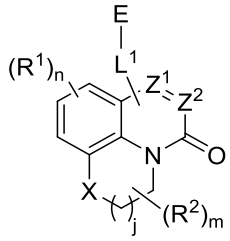
cancer, lung cancers and skin cancers. Finally, N-Ras mutations occur frequently in hepatocellular carcinoma.

**[0005]** There is a need for effective Ras inhibitors, which may provide a new class of anticancer compounds. These and other advantages will be apparent to those skilled in the art based upon embodiments and disclosures herein.

## SUMMARY

**[0005a]** In an aspect, there is provided a compound of Formula (XXI) or pharmaceutically acceptable salt thereof:




(XXI);

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;

$Z^1$ and $Z^2$ are independently $CR^6$ or N, with the proviso that at least one of $Z^1$ or $Z^2$ is $CR^6$ with $R^6$ being a bond to $L^1$;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, alkoxy, aryl, heteroaryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, and arylthio with the proviso that:

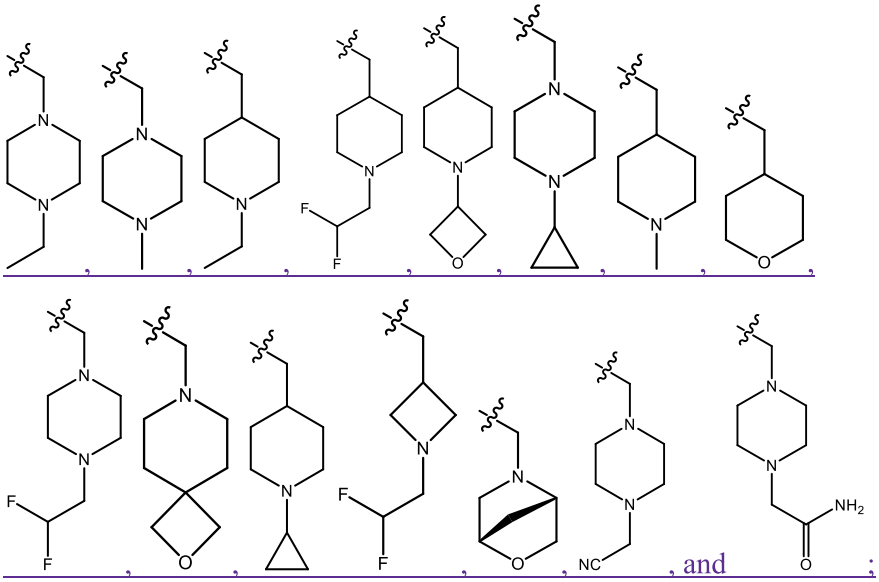
at least one $R^1$ is aryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

n is an integer from 1 to 3;

$R^2$ is selected from the group consisting of alkyl, amino, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, N-alkyl aminoalkyl, N,N-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, cyclopropyloxy, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, hydroxy, aryl, aralkyl, heteroaryl,

heteroarylalkyl, heterocyclyl, heterocyclylalkyl, and oxo any of which are optionally substituted;

wherein when j is 1, the heterocyclylalkyl is selected from:



or two $R^2$ together with the carbon atom to which they are attached form a spirocycle or heterocycle.

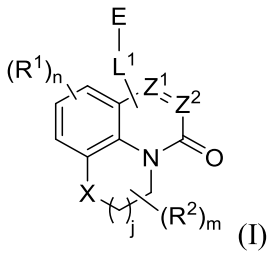
m is an integer from 0 to 6; and

$R^6$ is selected from the group consisting of hydrogen, alkyl, haloakyl, cyano, halo, alkoxy, aryl, heteroaryl, trifluoromethyl and bond to $L^1$.

**[0005b]** In another aspect, there is provided a a pharmaceutical composition comprising a compound as defined above or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

**[0005c]** In another aspect, there is provided the use of a compound as defined above or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer comprising a K-Ras G12C mutation, wherein a G12C mutant K-Ras is to be contacted with the compound as defined above to modulate the G12C mutant K-Ras.

**[0006]** In some ~~aspects~~examples, embodiments disclosed herein relate to compounds of Formula (I)



(I)

wherein:

X is O, $S(O)_p$ $CR^3R^4$, $NR^5$, or C(O), wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;

$Z^1$ and $Z^2$ are independently $CR^6$ or N, with the proviso that at least one of $Z^1$ or $Z^2$ is $CR^6$ with $R^6$ being a bond to $L^1$;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, alkoxy, aryl, heteroaryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, and arylthio with the proviso that:

at least one $R^1$ is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

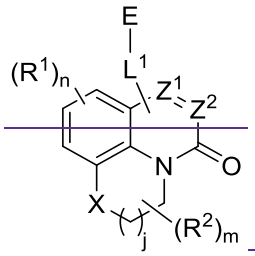
n is an integer from 1 to 3;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

## CLAIMS

What is claimed is:

1. A compound of Formula (XXI)



(XXI)

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;

$Z^1$ and $Z^2$ are independently $CR^6$ or N, with the proviso that at least one of $Z^1$ or $Z^2$ is $CR^6$ with $R^6$ being a bond to $L^1$;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, alkoxy, aryl, heteroaryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, and arylthio with the proviso that:

at least one $R^1$ is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

n is an integer from 1 to 3;

$R^2$ is selected from the group consisting of alkyl, amino, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, hydroxy, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, and oxo any of which are optionally substituted; or two $R^2$ together with the carbon atom to which they are attached form a spirocycle or heterocycle.

m is an integer from 0 to 6; and

$R^6$ is selected from the group consisting of hydrogen, alkyl, haloakyl, cyano, halo, alkoxy, aryl, heteroaryl, trifluoromethyl and bond to $L^1$.

2. The compound of claim 1, wherein X is S.

3. The compound of claim 1, wherein X is S=O or $SO_2$.

4. The compound of any one of claims 1 to 3, wherein j is 1.

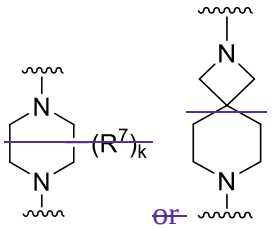
5. The compound of any one of claims 1 to 4, wherein m is 0.

6. The compound of any one of claims 1 to 4, wherein m is 1.

7. The compound of any one of claim 1 to 6, wherein $Z^1$ is $CR^6$ with $R^6$ being a bond to $L^1$.

8. The compound of any one of claims 1 to 7, wherein $Z^2$ is N.

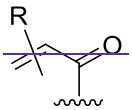
9. The compound of any one of claims 1 to 8, wherein $L^1$ is



or

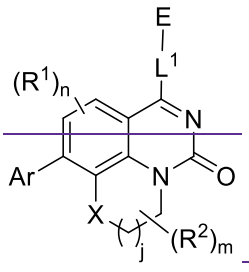
wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C{=}CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

10. The compound of any one of claims 1 to 9, wherein E is an acrylyl group having optional substitution R:



wherein R is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle.

11. A compound of Formula (XXIIa):



(XXIIa)

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

m is an integer from 0 to 6; and

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

12. The compound of claim 11, wherein X is S.

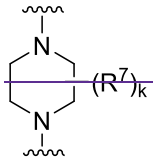
13. The compound of claim 11, wherein X is S=O or $SO_2$.

14. The compound of any one of claims 11 to 13, wherein j is 1.

15. The compound of any one of claims 11 to 14, wherein m is 0.

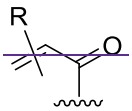
16. The compound of any one of claims 11 to 14, wherein m is 1.

17. The compound of any one of claims 11 to 16, wherein $L^1$ is




wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

18. The compound of any one of claims 11 to 17, wherein E is an acrylyl group having optional substitution R:

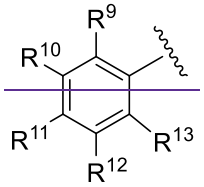



wherein R is selected from the group consisting of fluorine, methyl, and -$CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle.

19. The compound of any one of claims 11 to 18, wherein Ar creates axial asymmetry.

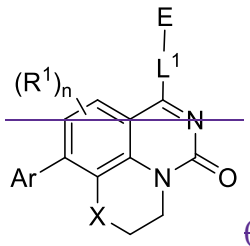
20. The compound of claim 19, wherein the compound is a single rotamer.

21. The compound of any one of claims 11 to 20 wherein Ar is:




wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

22. A compound of Formula (XXIII):




(XXIII)

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

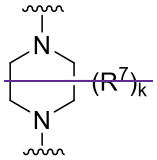
n is an integer from 0 to 2; and

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

23. The compound of claim 22, wherein X is S.

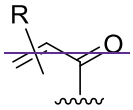
24. The compound of claim 22, wherein X is S=O or $SO_2$.

25. The compound of any one of claims 22 to 24, wherein $L^1$ is



wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

26. The compound of any one of claims 22 to 25, wherein E is an acrylyl group having optional substitution R:



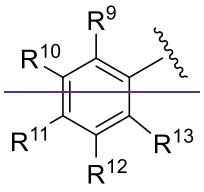
wherein R is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle.

27. The compound of claim 26, wherein optional substitution comprises monofluorination.

28. The compound of any one of claims 22 to 27, wherein Ar creates axial asymmetry.

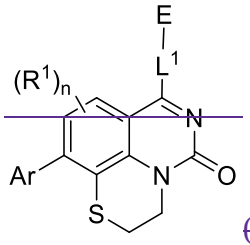
29. The compound of claim 28, wherein the compound is a single rotamer.

30. The compound of any one of claims 22 to 29, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

31. A compound of Formula (XXIV):



(XXIV)

wherein:

$L^1$ is linking group comprising at least one nitrogen atom;

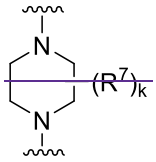
E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2; and

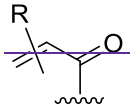
Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

32. The compound of claims 31, wherein $L^1$ is



wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

33. The compound of any one of claims 31 to 32, wherein E is an acrylyl group having optional substitution R:



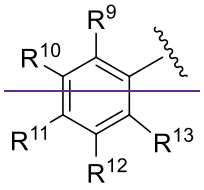
wherein R is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle.

34. The compound of claim 33, wherein optional substitution R is monofluorination.

35. The compound of any one of claims 31 to 34, wherein Ar creates axial asymmetry.

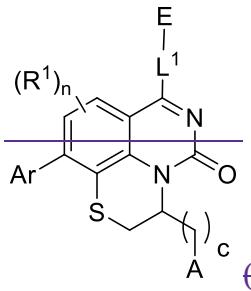
36. The compound of claim 35, wherein the compound is a single rotamer.

37. The compound of any one of claims 31 to 36, wherein Ar is:




wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

38. A compound of Formula (XXV):




(XXV)

wherein:

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

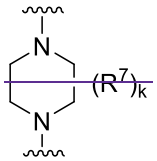
n is an integer from 0 to 2;

c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted; and

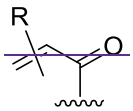
Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

39. The compound of claim 38, wherein $L^1$ is



wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

40. The compound of any one of claims 38 to 39, wherein E is an acrylyl group having optional substitution R:



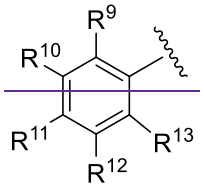
wherein R is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle.

41. The compound of claim 40, wherein optional substitution comprises monofluorination.

42. The compound of any one of claims 38 to 41, wherein Ar creates axial asymmetry.

43. The compound of claim 42, wherein the compound is a single rotamer.

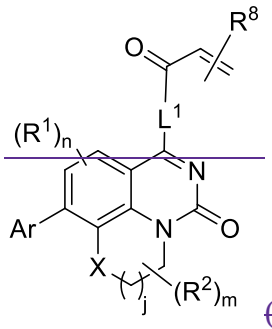
44. The compound of any one of claims 38 to 37 wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is

an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

45. A compound of Formula (XXVI):



(XXVI)

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;

$L^1$ is linking group comprising at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N* dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

m is an integer from 0 to 6;

$R^8$ is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle; and

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

46. The compound of claim 45, wherein X is S.

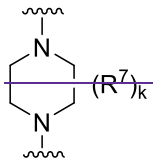
47. The compound of claim 45, wherein X is S=O or $SO_2$.

48. The compound of any one of claims 45 to 47, wherein j is 1.

49. The compound of any one of claims 45 to 48, wherein m is 0.

50. The compound of any one of claims 45 to 49, wherein m is 1.

51. The compound of any one of claims 45 to 50, wherein $L^1$ is

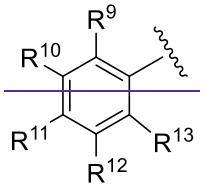


wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C{=}CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

52. The compound of any one of claims 45 to 51, wherein Ar creates axial asymmetry.

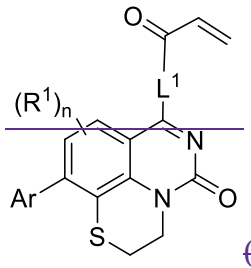
53. The compound of claim 52, wherein the compound is a single rotamer.

54. The compound of any one of claims 45 to 53, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

55. A compound of Formula (XXVII):



(XXVII)

wherein:

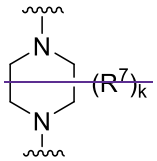
$L^1$ is linking group comprising at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2; and

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

56. The compound of claims 55, wherein $L^1$ is

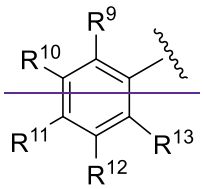


wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

57. The compound of any one of claims 55 to 56, wherein Ar creates axial asymmetry.

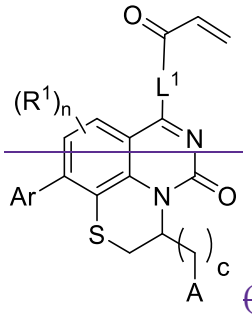
58. The compound of claim 57, wherein the compound is a single rotamer.

59. The compound of any one of claims 55 to 58, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

60. A compound of Formula (XXVIII):



(XXVIII)

wherein:

$L^1$ is linking group comprising at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

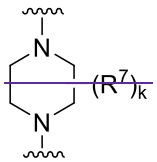
n is an integer from 0 to 2;

c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted; and

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

61. The compound of claim 60, wherein $L^1$ is

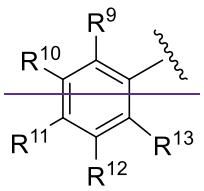


wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

62. The compound of any one of claims 60 to 61, wherein Ar creates axial asymmetry.

63. The compound of claim 62, wherein the compound is a single rotamer.

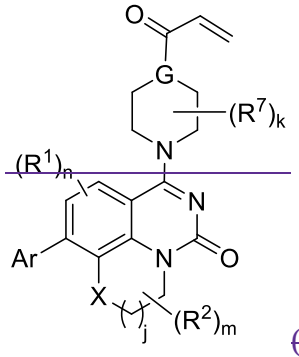
64. The compound of any one of claims 60 to 63, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any

two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

65. A compound of Formula (XXIX):

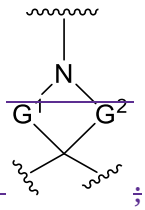


(XXIX)

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;



G is selected from the group consisting of N, CH, and ;

wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

n is an integer from 0 to 2;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

m is an integer from 0 to 6;

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C{=}CF_2$, cyano, propargyl,

$CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to G is optionally substituted.

66. The compound of claim 65, wherein X is S.

67. The compound of claim 65, wherein X is S=O or $SO_2$.

68. The compound of any one of claims 65 to 67, wherein j is 1.

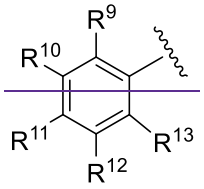
69. The compound of any one of claims 65 to 68, wherein m is 0.

70. The compound of any one of claims 65 to 68, wherein m is 1.

71. The compound of any one of claims 65 to 70, wherein Ar creates axial asymmetry.

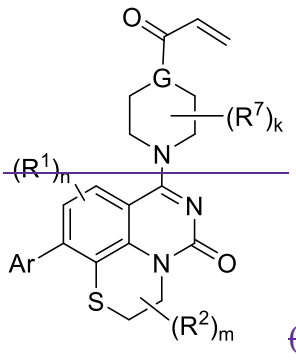
72. The compound of claim 71, wherein the compound is a single rotamer.

73. The compound of any one of claims 65 to 72, wherein Ar is:



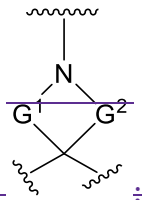

wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

74. A compound of Formula (XXX):




(XXX)

wherein:

G is selected from the group consisting of N, CH, and 

;

wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

n is an integer from 0 to 2;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

m is an integer from 0 to 4;

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^i$, wherein $R^i$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to G is optionally substituted.

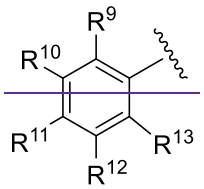
75. The compound of claim 74, wherein m is 0.

76. The compound of any one of claims 74, wherein m is 1.

77. The compound of any one of claims 74 to 76, wherein Ar creates axial asymmetry.

78. The compound of claim 77, wherein the compound is a single rotamer.

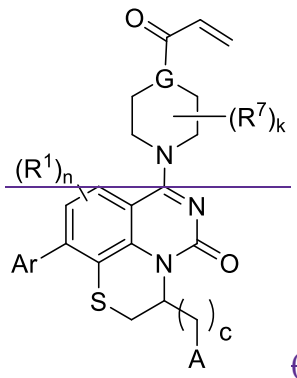
79. The compound of any one of claims 74 to 78, wherein Ar is:




wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is

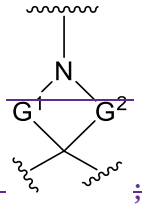
an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

80. A compound of Formula (XXXI):



(XXXI)

wherein:

G is selected from the group consisting of N, CH, and  ;

wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C{=}CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or

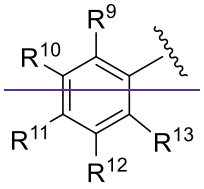
bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^i$, wherein $R^i$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to G is optionally substituted.

81. The compound of claim 80, wherein Ar creates axial asymmetry.

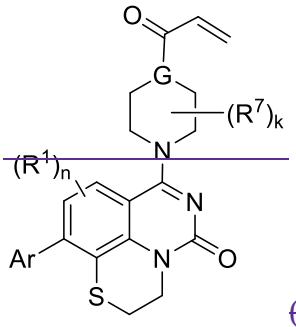
82. The compound of claim 81, wherein the compound is a single rotamer.

83. The compound of any one of claims 80 to 82, wherein Ar is:



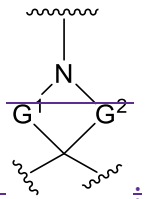

wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

84. A compound of Formula (XXXII):




(XXXII)

wherein:

G is selected from the group consisting of N, CH, and 

;

wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

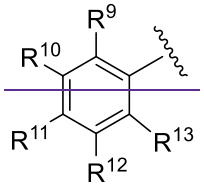
~~wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C{=}CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and~~

~~wherein the acrylyl moiety linked to G is optionally substituted.~~

~~85. The compound of claim 84, wherein Ar creates axial asymmetry.~~

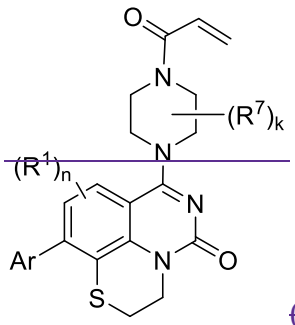
~~86. The compound of claim 85, wherein the compound is a single rotamer.~~

~~87. The compound of any one of claims 84 to 86, wherein Ar is:~~




~~wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.~~

~~88. A compound of Formula (XXXIII):~~




~~(XXXIII)~~

~~wherein:~~

~~each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;~~

~~n is an integer from 0 to 2;~~

~~Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;~~

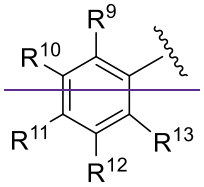
wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to N is optionally substituted.

89. The compound of claim 88, wherein Ar creates axial asymmetry.

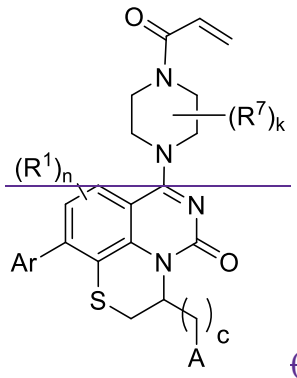
90. The compound of claim 89, wherein the compound is a single rotamer.

91. The compound of any one of claims 88 to 90, wherein Ar is:




wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

92. A compound of Formula (XXXIV):




(XXXIV)

wherein:

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

~~Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;~~

~~c is an integer from 0 to 4;~~

~~A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;~~

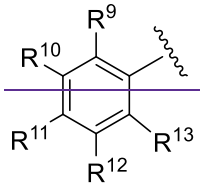
~~wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and~~

~~wherein the acrylyl moiety linked to N is optionally substituted.~~

~~93. The compound of claim 92, wherein Ar creates axial asymmetry.~~

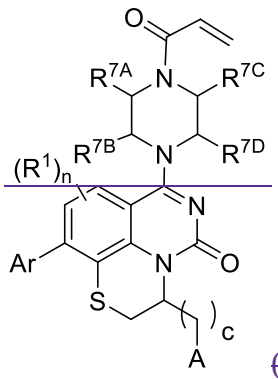
~~94. The compound of claim 93, wherein the compound is a single rotamer.~~

~~95. The compound of any one of claims 92 to 94, wherein Ar is:~~




~~wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.~~

96. A compound of Formula (XXXV):



(XXXV)

wherein:

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

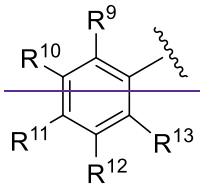
$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, alkyl, and cyanoalkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$.and

wherein the acrylyl moiety linked to N is optionally substituted.

97. The compound of claim 96, wherein Ar creates axial asymmetry.

98. The compound of claim 97, wherein the compound is a single rotamer.

99. The compound of any one of claims 96 to 98, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

100. The compound of any one of claims 96 to 99, wherein $R^{7B}$ is methyl.

101. The compound of claim 100, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *R* configuration.

102. The compound of claim 101, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *S* configuration.

103. The compound of any one of claims 96 to 102, wherein $R^{7C}$ is methyl.

104. The compound of claim 103, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *R* configuration.

105. The compound of claim 103, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *S* configuration.

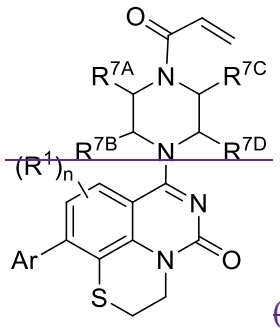
106. The compound of any one of claims 96 to 105, wherein $R^{7D}$ is hydrogen.

107. The compound of any one of claims 96 to 106, wherein $R^{7A}$ is cyanomethyl.

108. The compound of claim 107, wherein a stereogenic center created by the cyanomethyl group is in the *R* configuration.

109. The compound of claim 107, wherein a stereogenic center created by the cyanomethyl group is in the *S* configuration.

110. A compound of Formula (XXXVI):




(XXXVI)

wherein:

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

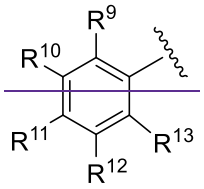
$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, alkyl, and cyanoalkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$;and

wherein the acrylyl moiety linked to N is optionally substituted.

111. The compound of claim 110, wherein Ar creates axial asymmetry.

112. The compound of claim 111, wherein the compound is a single rotamer.

113. The compound of any one of claims 110 to 112, wherein Ar is:




wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

114. The compound of any one of claims 110 to 113, wherein $R^{7B}$ is methyl.

115. The compound of claim 114, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *R* configuration.

116. The compound of claim 114, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *S*-configuration.

117. The compound of any one of claims 110 to 116, wherein $R^{7C}$ is methyl.

118. The compound of claim 117, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *R*-configuration.

119. The compound of claim 117, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *S*-configuration.

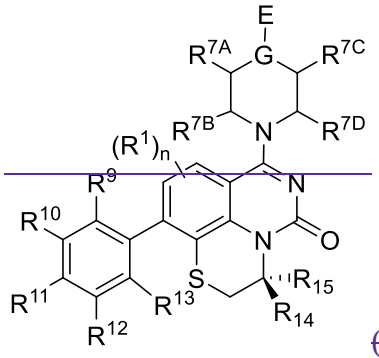
120. The compound of any one of claims 110 to 119, wherein $R^{7D}$ is hydrogen.

121. The compound of any one of claims 110 to 120, wherein $R^{7A}$ is cyanomethyl.

122. The compound of claim 121, wherein a stereogenic center created by the cyanomethyl group is in the *R*-configuration.

123. The compound of claim 121, wherein a stereogenic center created by the cyanomethyl group is in the *S*-configuration.

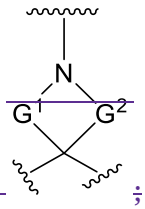
124. A compound of Formula (XXXVII):



(XXXVII)

wherein:

E is an electrophilic moiety;

G is selected from the group consisting of N, CH, and  ;

wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, alkyl, and cyanoalkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$.

wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted;

wherein $R^{14}$ and $R^{15}$ are selected from the group consisting of hydrogen, hydroxyl, amino, *N*-alkylamino, dialkylamino, *N*-alkylamino alkyl, *N*,*N*-dialkylamino, *N*,*N*-dialkylamino alkyl, cycloalkylamino, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl,

heteroarylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted, with the proviso that one of $R^{14}$ or $R^{15}$ is hydrogen; and

wherein E is optionally substituted.

125. The compound of claim 124, having axial asymmetry.

126. The compound of claim 124 or 125, wherein the compound is a single rotamer.

127. The compound of any one of claims 124 to 126, wherein $R^{7B}$ is methyl.

128. The compound of claim 127, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *R* configuration.

129. The compound of claim 127, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *S* configuration.

130. The compound of any one of claims 124 to 129, wherein $R^{7C}$ is methyl.

131. The compound of claim 130, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *R* configuration.

132. The compound of claim 130, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *S* configuration.

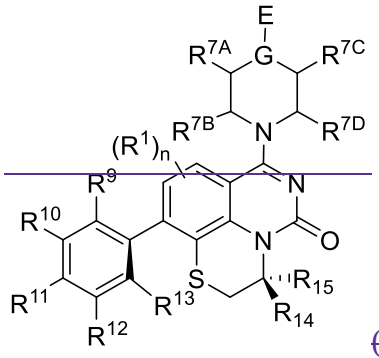
133. The compound of any one of claims 124 to 132, wherein $R^{7D}$ is hydrogen.

134. The compound of any one of claims 124 to 133, wherein $R^{7A}$ is cyanomethyl.

135. The compound of claim 134, wherein a stereogenic center created by the cyanomethyl group is in the *R* configuration.

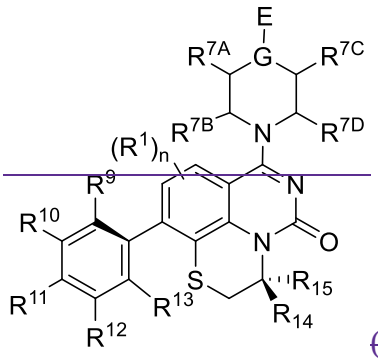
136. The compound of claim 134, wherein a stereogenic center created by the cyanomethyl group is in the *S* configuration.

137. The compound of any one of claims 124 to 136, wherein the compound is a single rotamer of Formula (XXXVIIa):



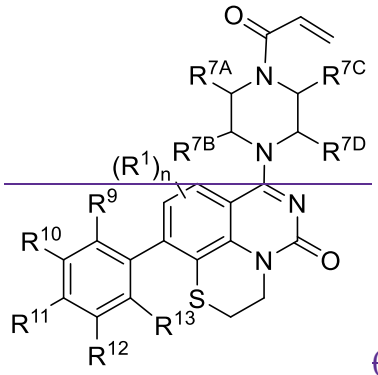

(XXXVIIa)

138. The compound of any one of claims 124 to 136, wherein the compound is a single rotamer of Formula (XXXVIIb):



(XXXVIIb)

139. A compound of Formula (XXXVIII):



(XXXVIII)

wherein:

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, alkyl, and cyanoalkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$.

wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

wherein the acrylyl moiety linked to N is optionally substituted.

140. The compound of claim 139, having axial asymmetry.

141. The compound of claim 139 or 140, wherein the compound is a single rotamer.

142. The compound of any one of claims 139 to 141, wherein $R^{7B}$ is methyl.

143. The compound of claim 142, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *R* configuration.

144. The compound of claim 142, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *S*-configuration.

145. The compound of any one of claims 139 to 144, wherein $R^{7C}$ is methyl.

146. The compound of claim 145, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *R*-configuration.

147. The compound of claim 145, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *S*-configuration.

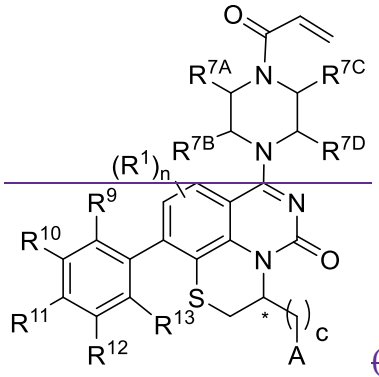
148. The compound of any one of claims 139 to 147, wherein $R^{7D}$ is hydrogen.

149. The compound of any one of claims 139 to 148, wherein $R^{7A}$ is cyanomethyl.

150. The compound of claim 149, wherein a stereogenic center created by the cyanomethyl group is in the *R*-configuration.

151. The compound of claim 149, wherein a stereogenic center created by the cyanomethyl group is in the *S*-configuration.

152. A compound of Formula (XXXIX):



(XXXIX)

wherein * is a stereogenic center;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, alkyl, and cyanoalkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$.

wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

c is an integer from 0 to 4;

~~A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted; and~~

~~wherein the acrylyl moiety linked to N is optionally substituted.~~

~~153. The compound of claim 152, having axial asymmetry.~~

~~154. The compound of claim 152 or 153, wherein the compound is a single rotamer.~~

~~155. The compound of any one of claims 152 to 154, wherein $R^{7B}$ is methyl.~~

~~156. The compound of claim 155, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *R* configuration.~~

~~157. The compound of claim 155, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *S* configuration.~~

~~158. The compound of any one of claims 152 to 157, wherein $R^{7C}$ is methyl.~~

~~159. The compound of claim 158, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *R* configuration.~~

~~160. The compound of claim 158, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *S* configuration.~~

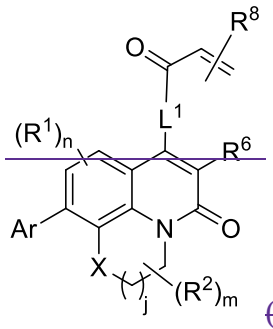
~~161. The compound of any one of claims 152 to 160, wherein $R^{7D}$ is hydrogen.~~

~~162. The compound of any one of claims 152 to 161, wherein $R^{7A}$ is cyanomethyl.~~

~~163. The compound of claim 162, wherein a stereogenic center created by the cyanomethyl group is in the *R* configuration.~~

~~164. The compound of claim 162, wherein a stereogenic center created by the cyanomethyl group is in the *S* configuration.~~

~~165. A compound of Formula (XL):~~




~~(XL)~~

~~wherein:~~

~~X is $S(O)_p$, wherein p is an integer from 0 to 2;~~

j is an integer from 0 to 2;

$L^1$ is linking group comprising at least one nitrogen atom;

each $R^1$ is is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

n is an integer from 0 to 2;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

m is an integer from 0 to 6;

$R^6$ is is selected from the group consisting of hydrogen, alkyl, haloakyl, cyano, halo, alkoxy, aryl, heteroaryl, and trifluoromethyl;

$R^8$ is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle; and

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

166. The compound of claim 165, wherein X is S.

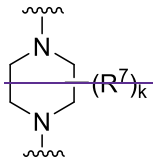
167. The compound of claim 165, wherein X is S=O or $SO_2$.

168. The compound of any one of claims 165 to 167, wherein j is 1.

169. The compound of any one of claims 165 to 168, wherein m is 0.

170. The compound of any one of claims 165 to 168, wherein m is 1.

171. The compound of any one of claims 165 to 170, wherein $L^1$ is



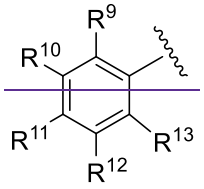

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$,, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$, wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or

bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^i$, wherein $R^i$ is H, methyl or trifluoromethyl.

172. The compound of any one of claims 165 to 171, wherein Ar creates axial asymmetry.

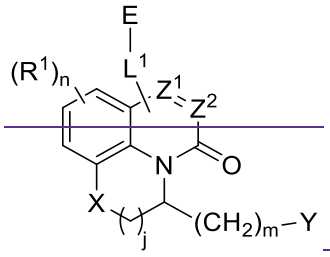
173. The compound of claim 172, wherein the compound is a single rotamer.

174. The compound of any one of claims 165 to 173, wherein Ar is:




wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

175. The compound of claim 165, given by Formula XLI:




(XLI)

wherein:

Y is selected from the group consisting of hydrogen; *N*-linked heteroaromatic ring; *N*-linked azetidinyl optionally substituted with fluorine, CO-NR'R'', or spiro-linked oxetane; $OR^a$; and $Z^3R^bR^c$;

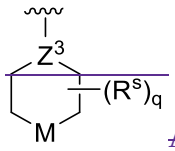
R' and R'' are independently hydrogen, alkyl or cycloalkyl;

$Z^3$ is CH, COH, or N;

m is an integer from 1 to 5;

$R^a$ is hydrogen, methyl, ethyl trifluoromethyl, heterocyclyl, or heterocyclylalkyl;

$R^b$ and $R^c$ are independently selected from alkyl, alkyl having one or more fluorine substitutions, cycloalkyl, oxetanyl, and *N*-methyl prolinyl; or $R^b$ and $R^c$ combine to form a cyclic structure A1:




A1

wherein q is an integer from 1 to 4; M is selected from a bond, O, S, SO, $SO_2$, $CH_2$, NH, NMe, N-ethyl, N-oxetanyl, and N-cyclopropyl, wherein each C-H of each alkylene, alkyl or cycloalkyl group is independently optionally substituted with a fluorine atom;

each $R^s$ is independently fluorine, oxo, alkoxy, or CO-NR'R'', or any two $R^s$ combine to form a 1 to 3 carbon atom bridge, wherein the 1 to 3 carbon atom bridge is optionally substituted with one or more fluorine atoms;

each R' and R'' is independently hydrogen, alkyl or cycloalkyl;

j is an integer from 0 to 2;

$Z^1$ and $Z^2$ are independently $CR^6$ or N, with the proviso that at least one of $Z^1$ or $Z^2$ is $CR^6$ with $R^6$ being a bond to $L^1$;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is independently selected from the group consisting of acyl, alkyl, carboxamide, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, alkoxy, aryl, heteroaryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, cycloalkyl, heterocyclyl, and arylthio with the proviso that at least one $R^1$ is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

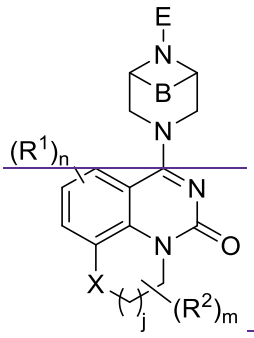
n is an integer from 1 to 3;

m is an integer from 0 to 6;

$R^3$, $R^4$, and $R^5$ are each independently selected from the group consisting of hydrogen alkyl, halo, alkoxy, aryl, heteroaryl, and cycloalkyl, any of which are optionally substituted; and

$R^6$ is selected from the group consisting of hydrogen, alkyl, haloakyl, cyano, halo, alkoxy, aryl, heteroaryl, trifluoromethyl and bond to $L^1$, and pharmaceutically acceptable salts thereof.

176. The compound of claim 173, having the formula XLII



(XLII)

wherein:

X is O, $S(O)_p$, $CR^3R^4$, $NR^5$, or C(O), wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;

B is bridging group comprising 1 to 3 carbon atoms, wherein any one carbon atom is optionally replaced by O, S, $SO_2$, or N-alkyl;

E is an electrophilic moiety;

each $R^1$ is independently selected from the group consisting of acyl, alkyl, carboxamide, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, alkoxy, aryl, heteroaryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, cycloalkyl, heterocyclyl, and arylthio with the proviso that:

at least one $R^1$ is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

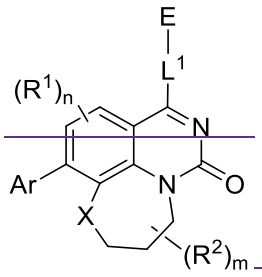
n is an integer from 1 to 3;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, amido, amido alkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

m is an integer from 0 to 6;

$R^3$, $R^4$, and $R^5$ are each independently selected from the group consisting of hydrogen alkyl, halo, alkoxy, aryl, heteroaryl, and cycloalkyl, any of which are optionally substituted, and pharmaceutically acceptable salts thereof.

177. A compound of Formula (XLIII) or pharmaceutically acceptable salt thereof:



(XLIII)

wherein:

X is O or S;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

Ar is selected from the group consisting of aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

n is an integer from 1 to 2;

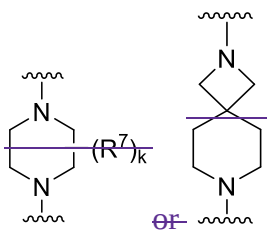
each $R^2$ is independently selected from the group consisting optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CHR'R'', -OR', -SR', and -NR',R''; wherein each R' or R'' is selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, hydroxy, cycloalkoxy, cyano, cyanoalkyl, amido, amidoalkyl, *N*-alkylamido, *N*-alkylamidoalkyl, *N*,*N*-dialkylamido, *N*,*N*-dialkylamidoalkyl, amino, aminoalkyl, *N*-alkyl amino, *N*-alkyl aminoalkyl, *N*,*N*-dialkylamino, and *N*,*N*-dialkylaminoalkyl, any of which are optionally substituted; or any two R' and R'' combine to form 3-7-membered ring, optionally comprising 1 or 2 heteroatoms selected from N, O, or S; or any two $R^2$ combine to form a spirocycle comprising 0 to 2 heteroatoms selected from N, O, or S; and

m is an integer from 0 to 6.

178. The compound of claim 177, wherein m is 0-2.

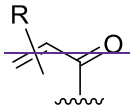
179. The compound of claim 177, wherein m is 1 or 2.

180. The compound of any one of claims 177 to 179, wherein $L^1$ is



wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from methyl, and cyanomethyl, or any two $R^7$ combine to form a bridge or spirocycle structure optionally comprising a heteroatom in the bridge or spirocycle selected from S, $SO_2$, O or N, and wherein the bridge or spirocycle structure is optionally substituted with oxo.

181. The compound of any one of claims 177 to 180, wherein E is an acrylyl group having optional substitution R:

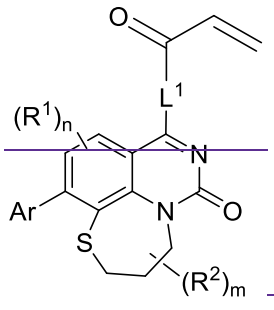



wherein R is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle.

182. The compound of any one of claims 177 to 181, wherein X is S.

183. The compound of any one of claims 177 to 182, wherein Ar is a phenyl optionally substituted with one or more alkyl, cycloalkyl, fluoro, chloro, bromo, iodo, trifluoromethyl or cyano.

184. A compound of Formula (XLIV) or pharmaceutically acceptable salt thereof:




(XLIV)

wherein:

$L^1$ is linking group comprising at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cyclopropyl, halo, haloalkyl, trifluoromethyl, alkoxy,

n is 1 or 2;

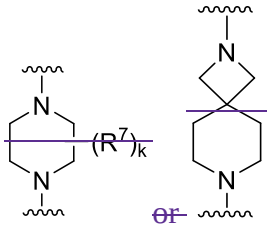
each $R^2$ is independently selected from the group consisting optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-CHR'R''$, $-OR'$, $-SR'$, and $-NR',R''$; wherein each R' or R'' is selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, hydroxy, cycloalkoxy, cyano, cyanoalkyl, amido, amidoalkyl, *N*-alkylamido, *N*-alkylamidoalkyl, *N*,*N*-dialkylamido, *N*,*N*-dialkylamidoalkyl, amino, aminoalkyl, *N*-alkyl amino, *N*-alkyl aminoalkyl, *N*,*N*-dialkylamino, and *N*,*N*-dialkylaminoalkyl, any of which are optionally substituted; or any two R' and R'' combine

to form 3-7-membered ring, optionally comprising 1 or 2 heteroatoms selected from N, O, or S; or any two $R^2$ combine to form a spirocycle comprising 0 to 2 heteroatoms selected from N, O, or S;

m is 1 or 2; and

Ar is a phenyl group optionally substituted with one or more alkyl, cycloalkyl, fluoro, chloro, bromo, iodo, trifluoromethyl or cyano.

185. The compound of claim184, wherein $L^1$ is



or

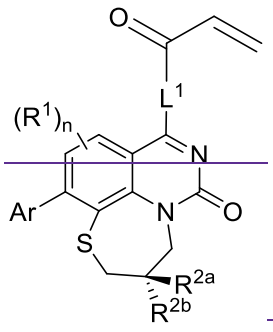
wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from methyl, and cyanomethyl, or any two $R^7$ combine to form a bridge or spirocycle structure optionally comprising a heteroatom in the bridge or spirocycle selected from S, $SO_2$, O or N, and wherein the bridge or spirocycle structure is optionally substituted with oxo.

186. The compound of claim 185, wherein n is 1 and $R^1$ is ortho to Ar.

187. The compound of claim 186, wherein $R^1$ is chloro or trifluoromethyl.

188. The compound of any one of claims 185 to 187, wherein Ar is a phenyl ring comprising 1 to 3 fluorine substitutions.

189. A compound of Formula (XLV) or pharmaceutically acceptable salt thereof:



(XLV)

wherein:

$L^1$ is linking group comprising at least one nitrogen atom;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cyclopropyl, halo, haloalkyl, trifluoromethyl, alkoxy,

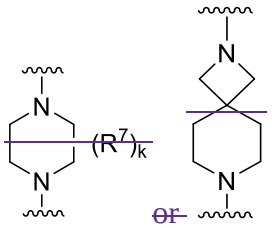
n is 1 or 2;

$R^{2a}$ and $R^{2b}$ are independently selected from the group consisting of hydrogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl,

CHR'R'', -OR', -SR', and -NR',R''; wherein each R' or R'' is selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, hydroxy, cycloalkoxy, cyano, cyanoalkyl, amido, amidoalkyl, *N*-alkylamido, *N*-alkylamidoalkyl, *N*,*N*-dialkylamido, *N*,*N*-dialkylamidoalkyl, amino, aminoalkyl, *N*-alkyl amino, *N*-alkyl aminoalkyl, *N*,*N*-dialkylamino, *N*,*N*-dialkylaminoalkyl, any of which are optionally substituted; or R' and R'' combine to form 3-7-membered ring, optionally comprising 1 or 2 heteroatoms selected from N, O, or S, or $R^{2a}$ and $R^{2b}$ combine to form a spirocycle comprising 0 to 2 heteroatoms selected from N, O, or S; and

Ar is a phenyl optionally substituted with one or more alkyl, cycloalkyl, fluoro, chloro, bromo, iodo, trifluoromethyl or cyano.

190. The compound of claim 189, wherein $L^1$ is



or

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from methyl, and cyanomethyl, or any two $R^7$ combine to form a bridge or spirocycle structure optionally comprising a heteroatom in the bridge or spirocycle selected from S, $SO_2$, O or N, and wherein the bridge or spirocycle structure is optionally substituted with oxo.

191. The compound of any one of claims 189 to 190 wherein n is 1 and $R^1$ is ortho to Ar.

192. The compound of claim 539, wherein $R^1$ is chloro or trifluoromethyl.

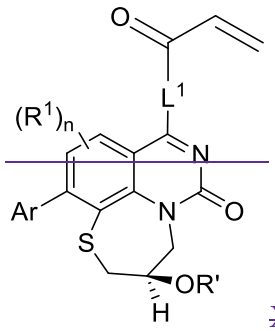
193. The compound of any one of claims 189 to 192, wherein Ar is a phenyl ring comprising 1 to 3 fluorine substitutions.

194. The compound of any one of claims 189 to 193, wherein $R^{2a}$ is hydrogen and $R^{2b}$ is not hydrogen.

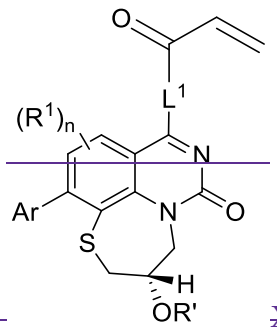
195. The compound of any one of claims 189 to 193, wherein $R^{2a}$ is hydrogen and $R^{2b}$ is not hydrogen.

196. The compound of any one of claims 189 to 193, wherein $R^{2a}$ and $R^{2b}$ combine to form a spirocyclic carbocycle or heterocycle.

197. The compound of any one of claims 189 to 195 having the structure of formula XLVa or XLVb :

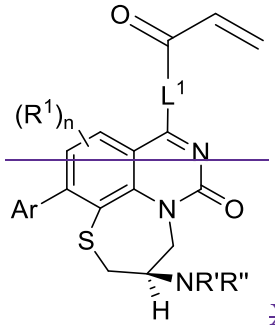



XLVa

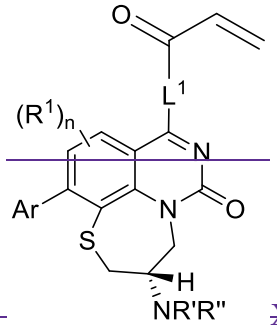



XLVb.

198. The compound of any one of claims 189 to 195 having the structure of formula XLVc or XLVd :

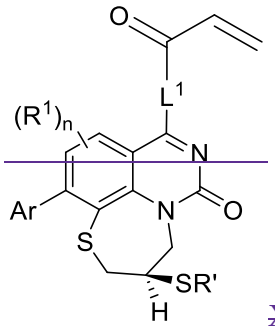



XLVc

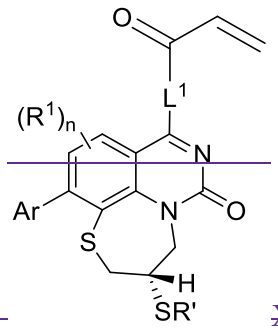



XLVd.

199. The compound of any one of claims 189 to 195 having the structure of formula XLVe or XLVf :

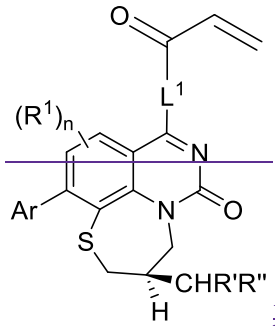



XLVe

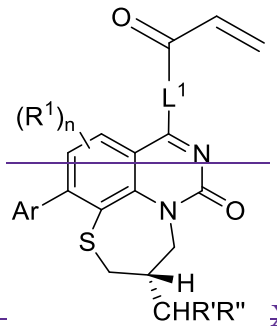



XLVf.

200. The compound of any one of claims 189 to 195 having the structure of formula XLVg or XLVh :

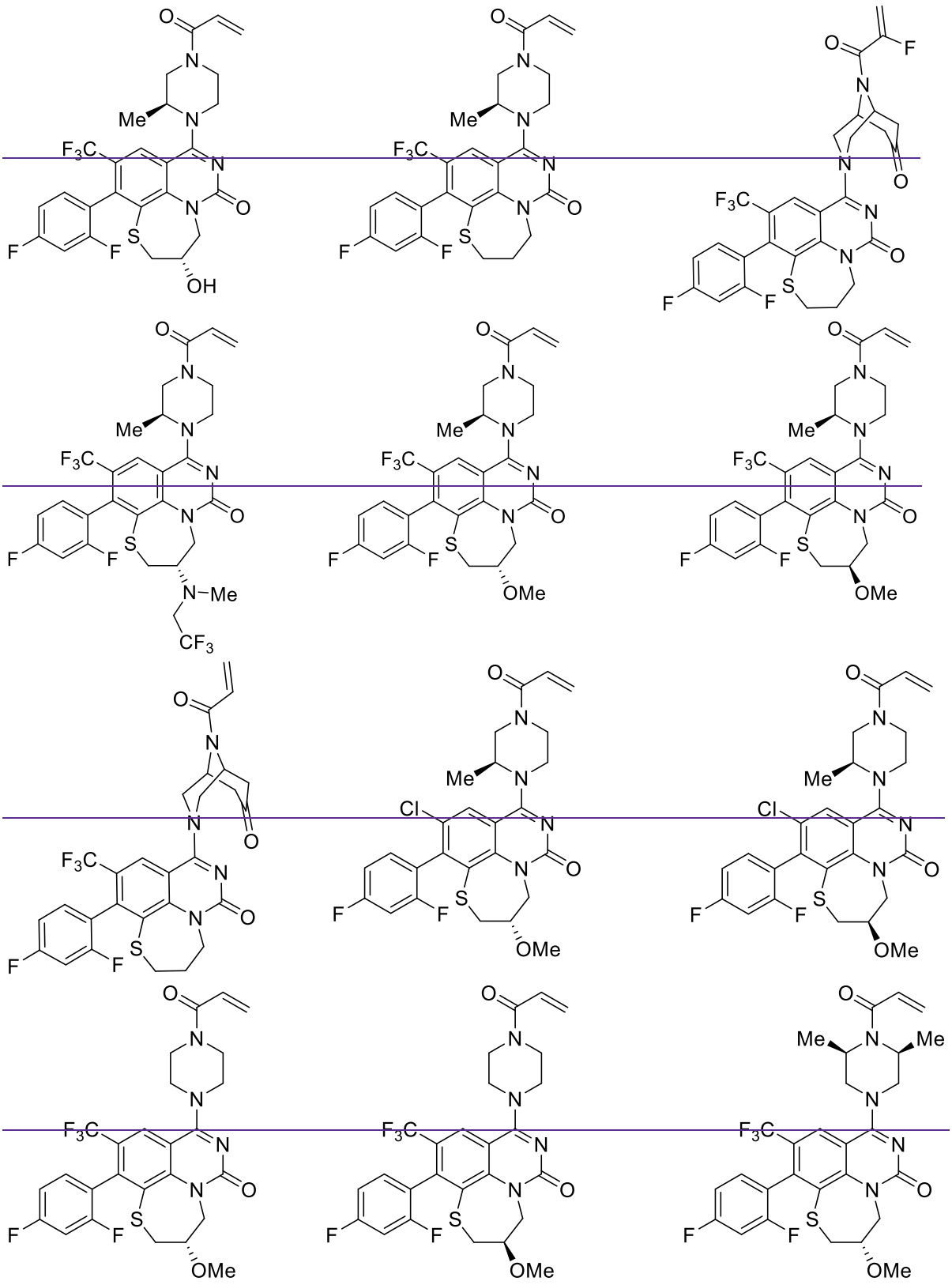


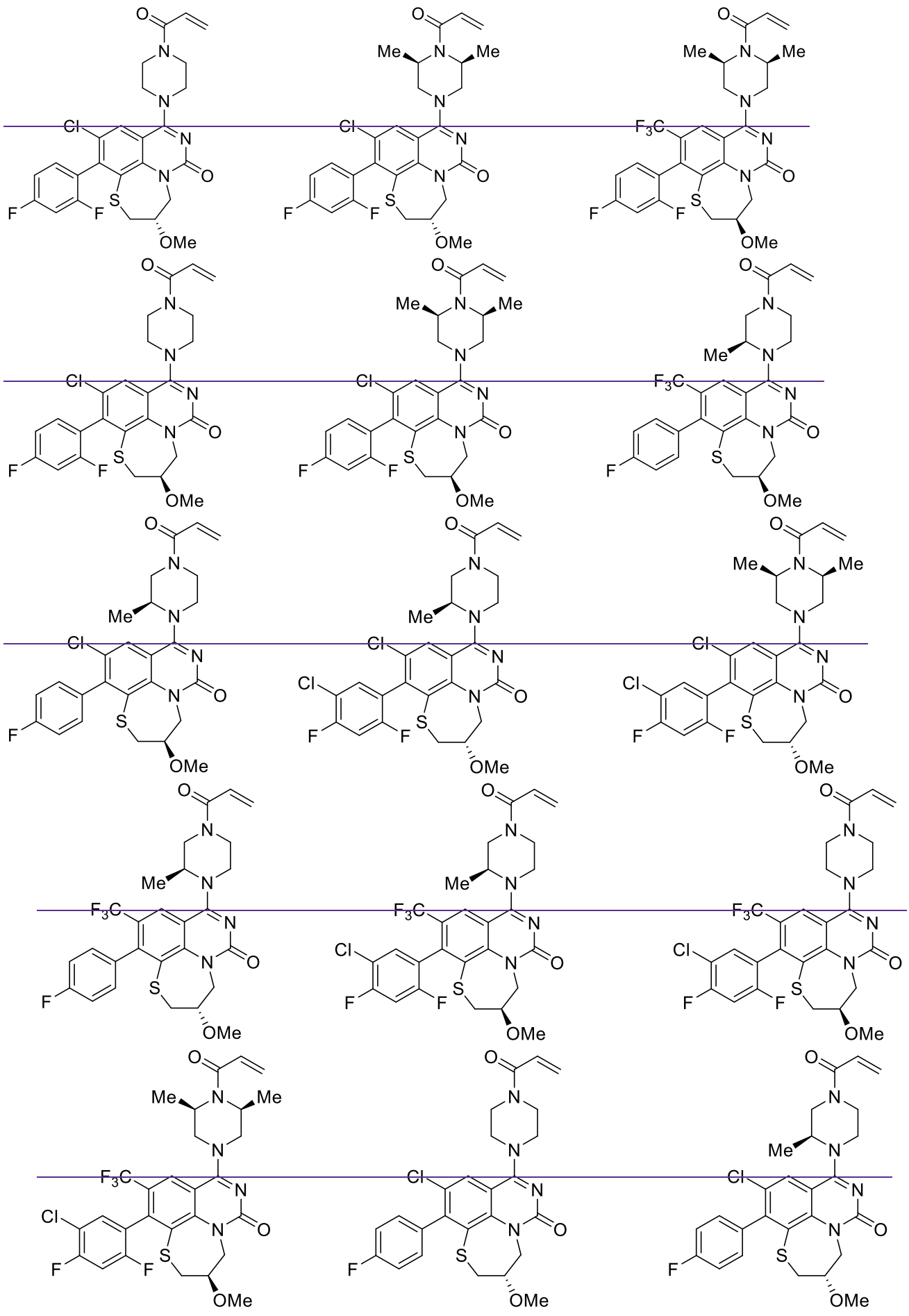

XLVg

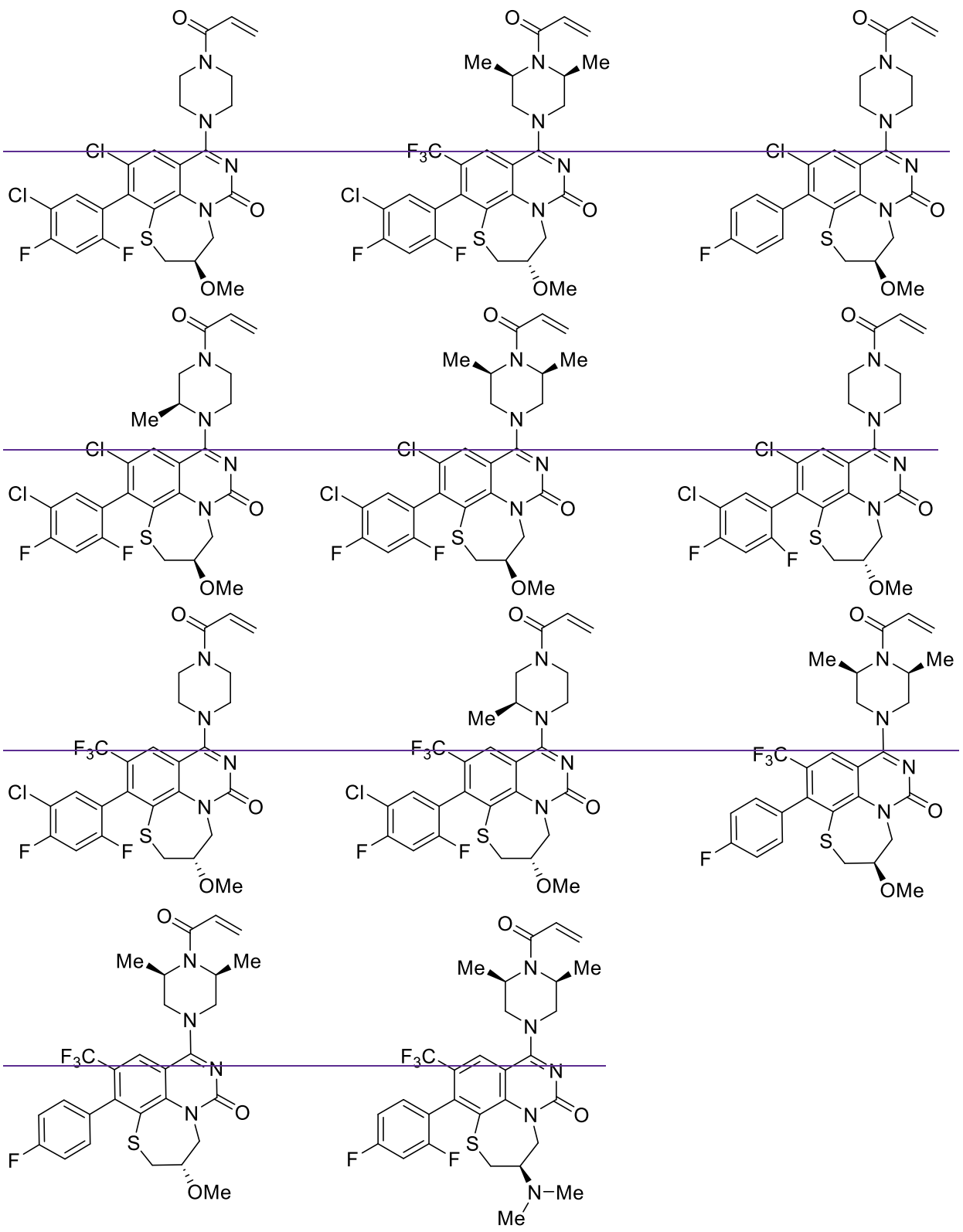


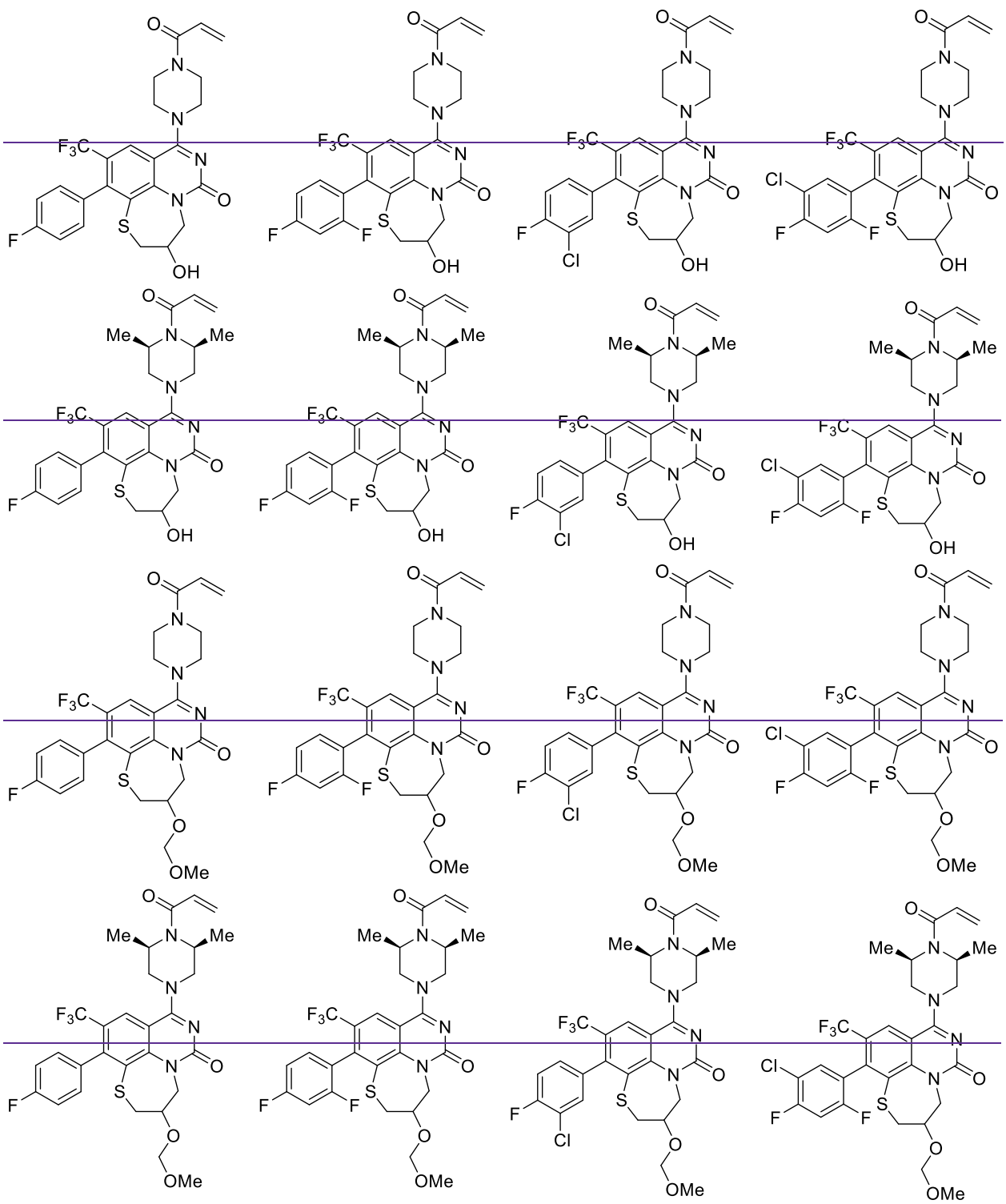

XLVh.

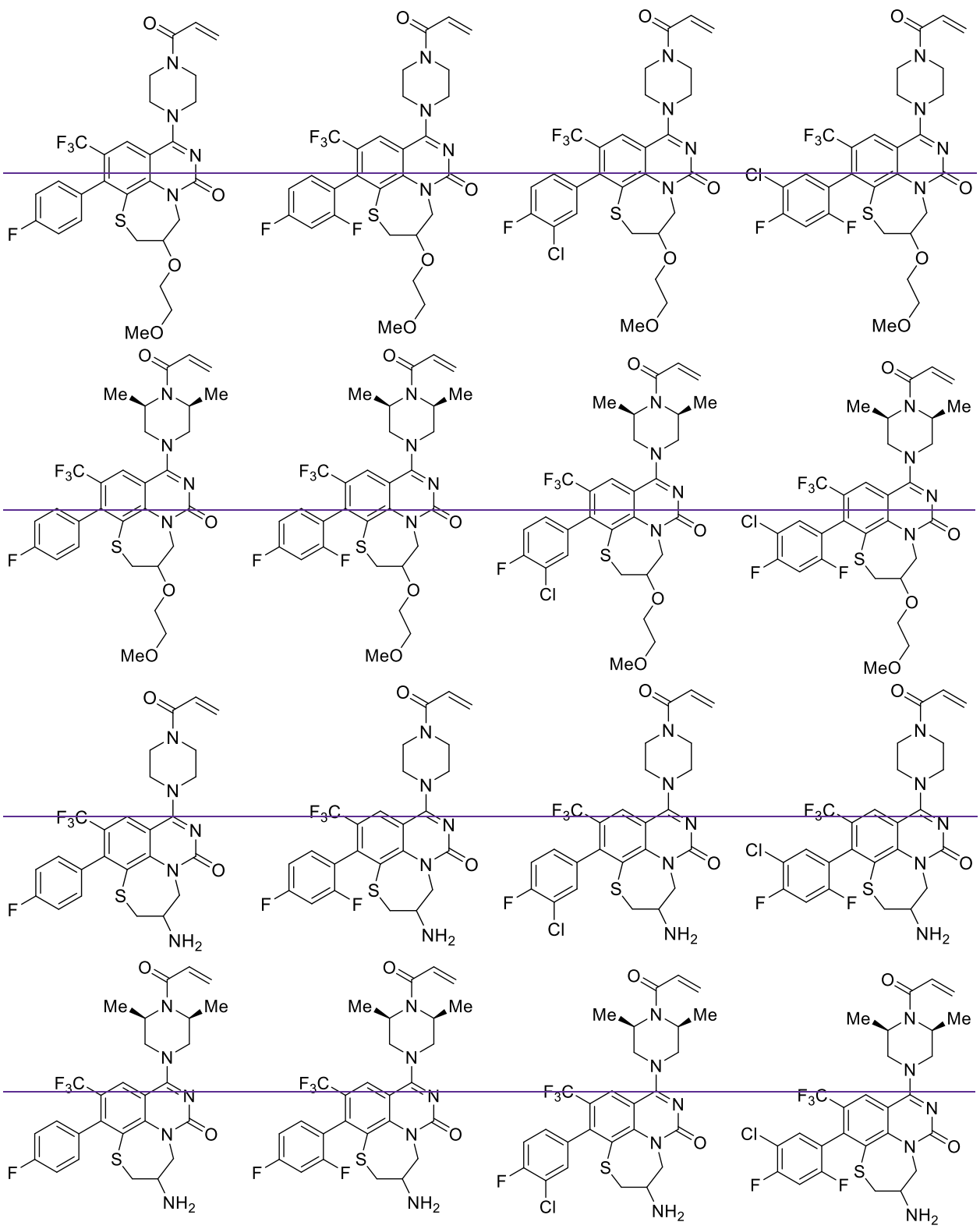
201. A compounds selected from:

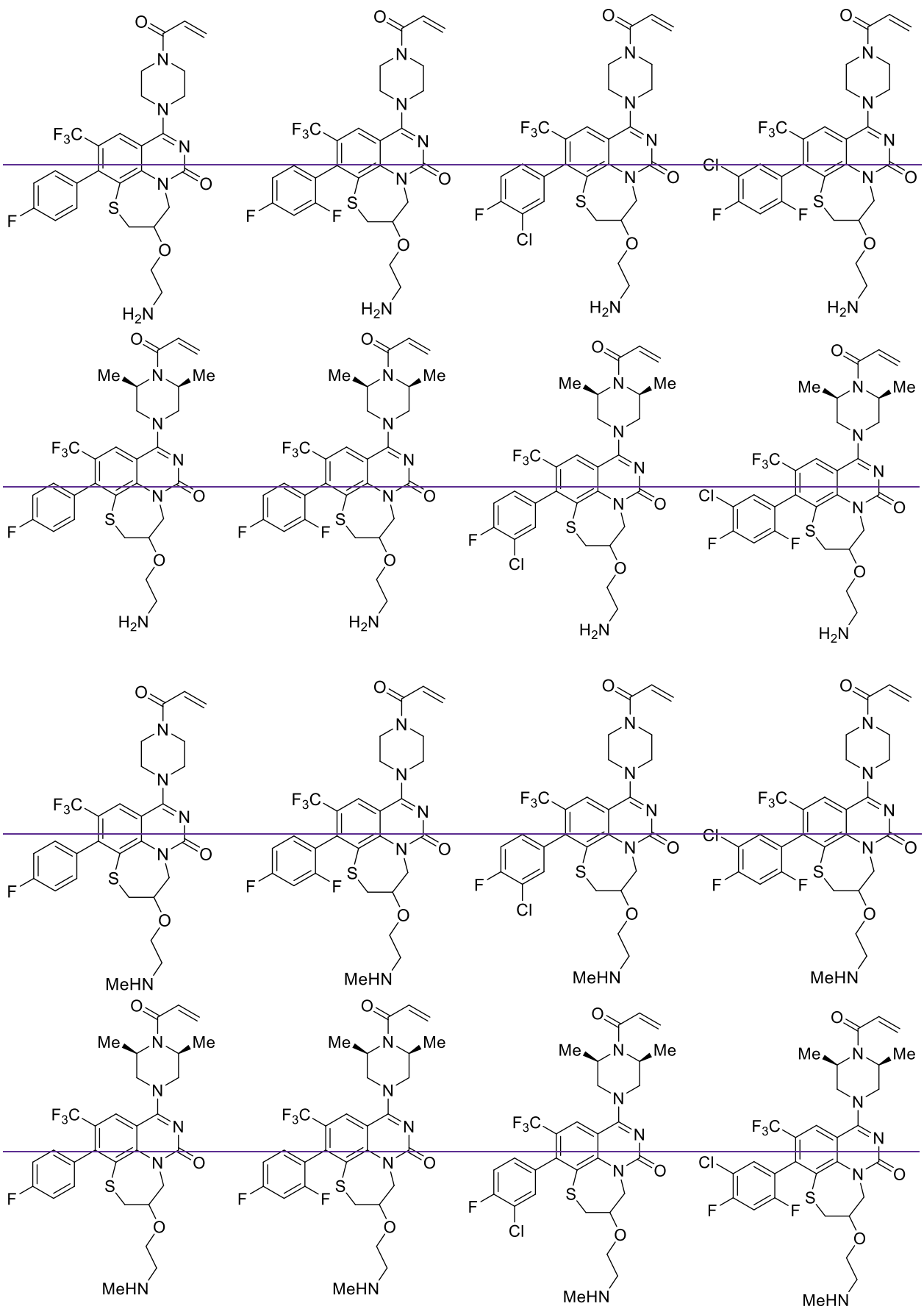


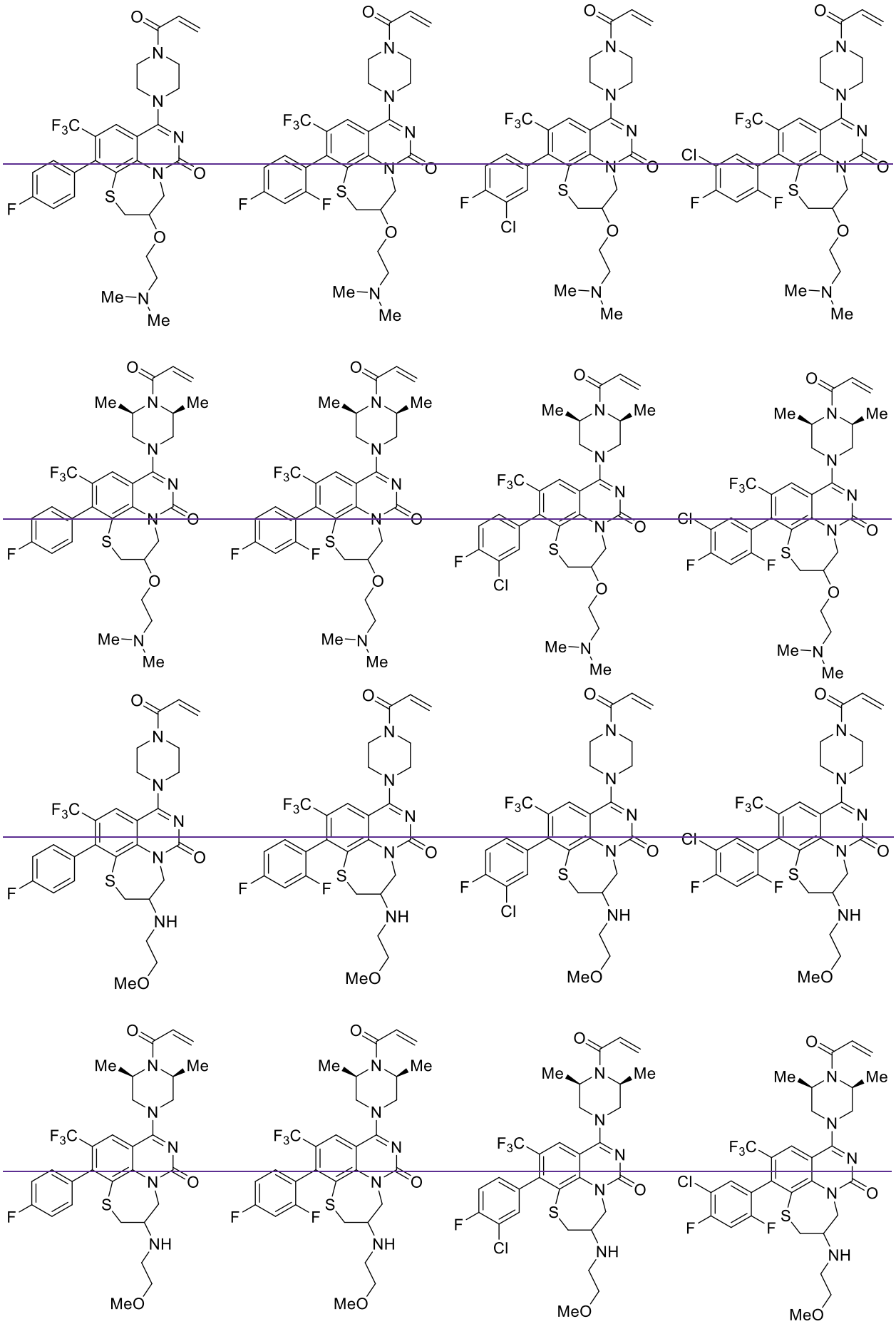


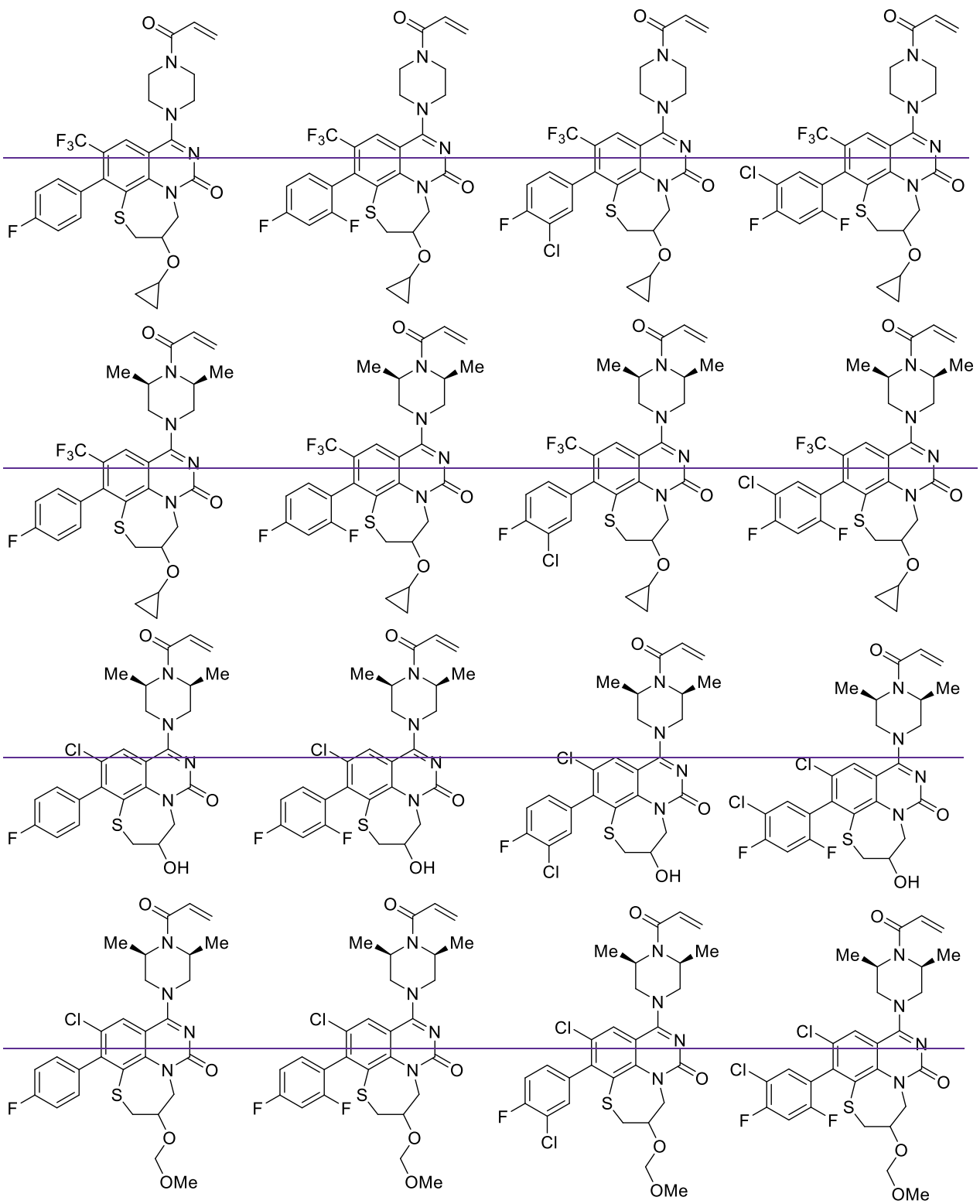


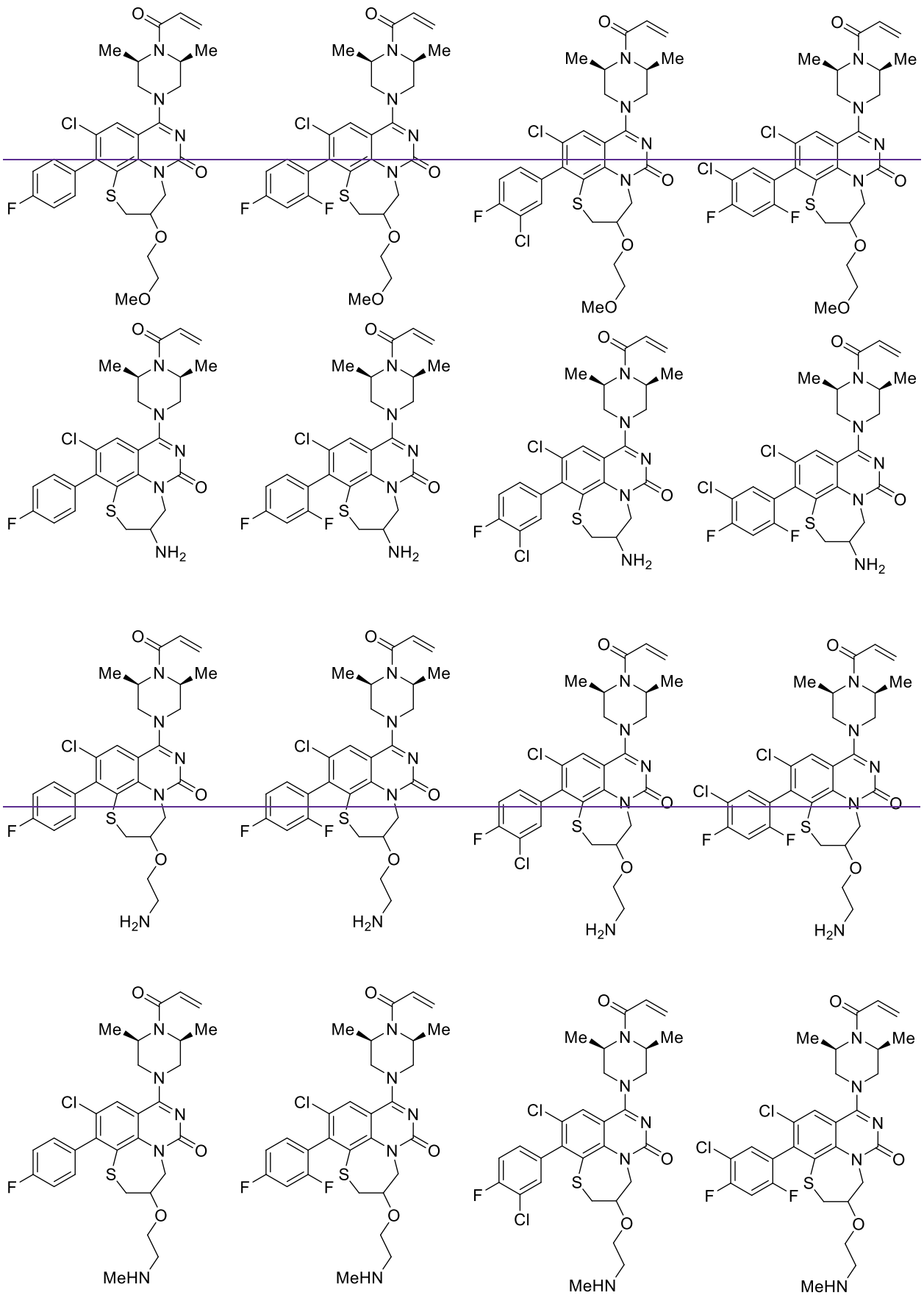


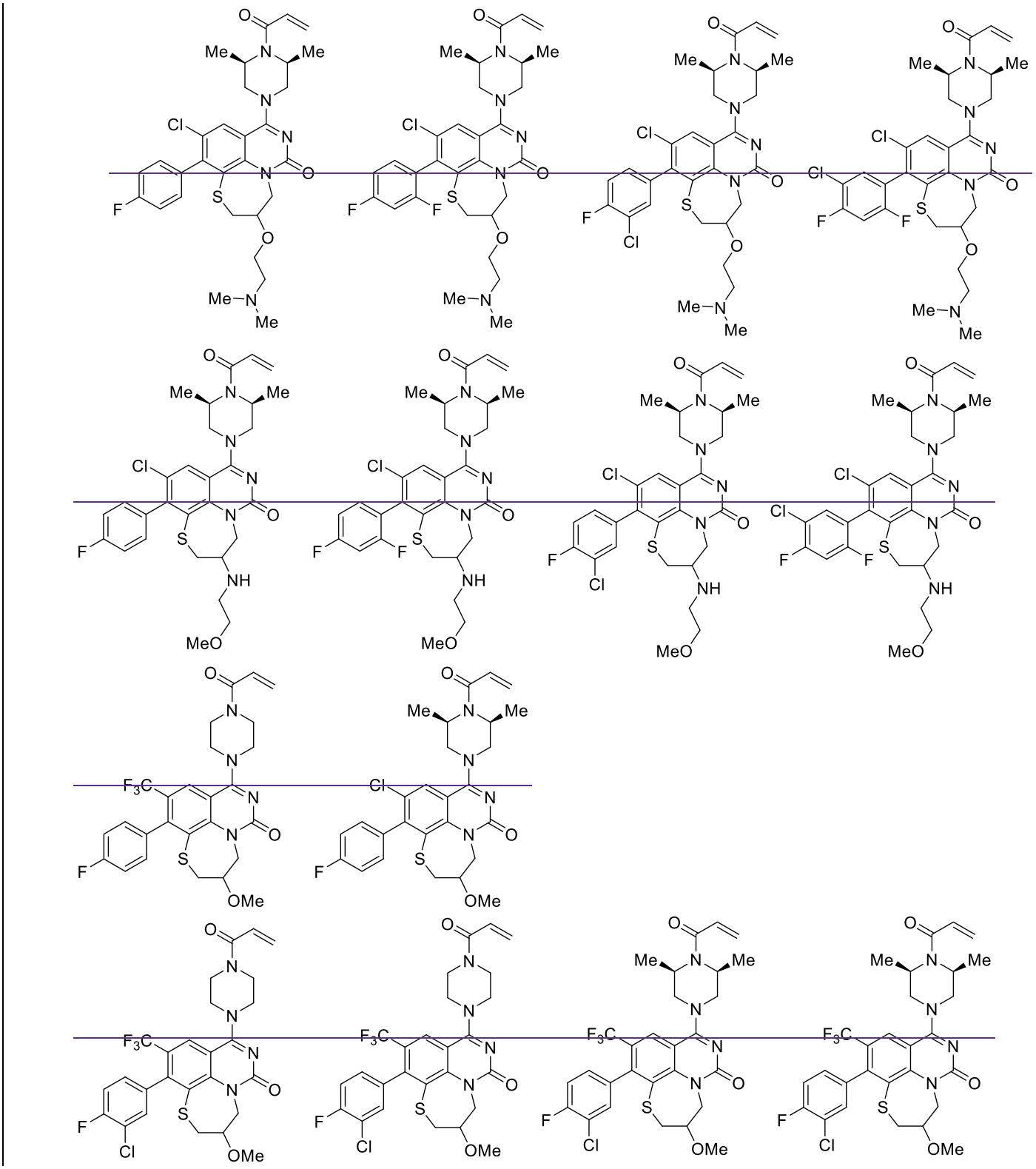


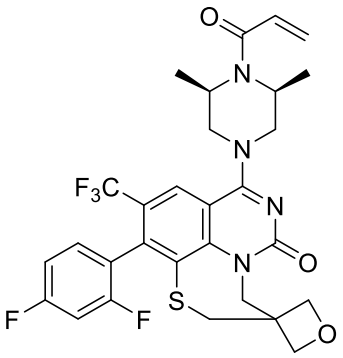


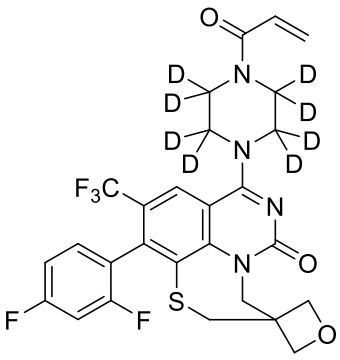


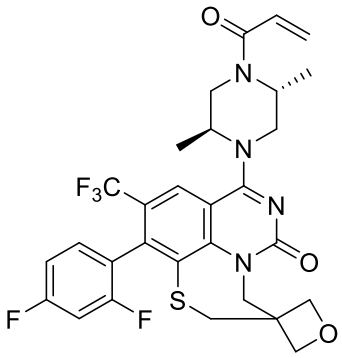


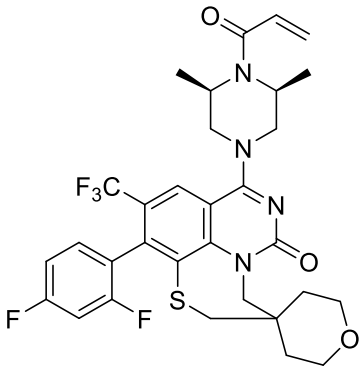


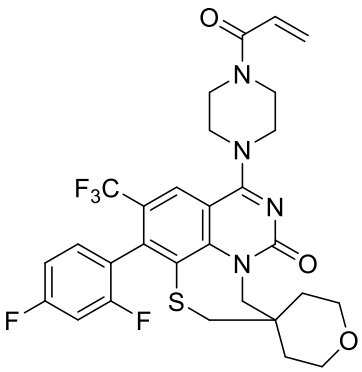


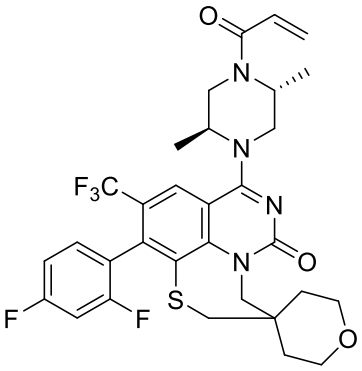


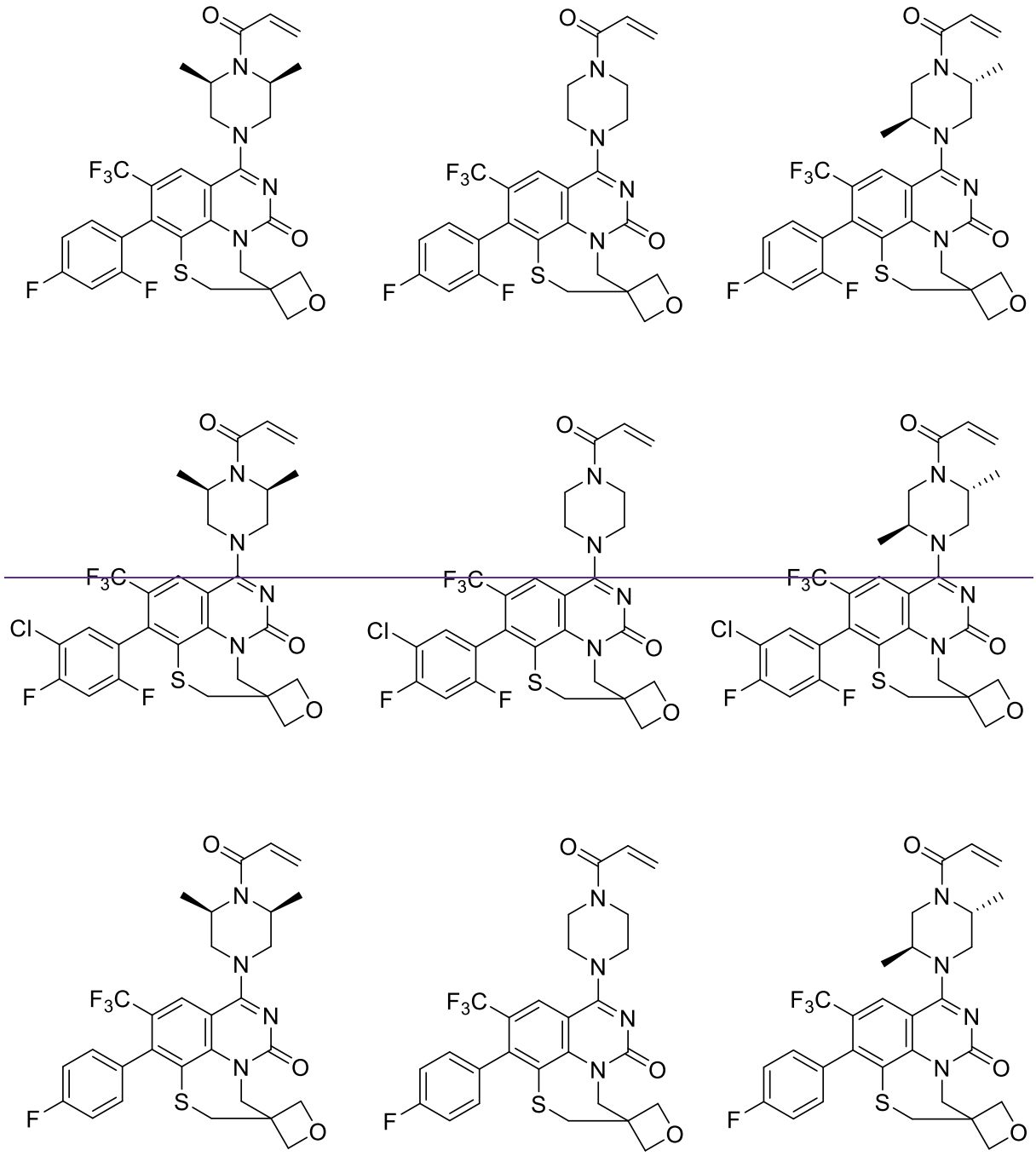


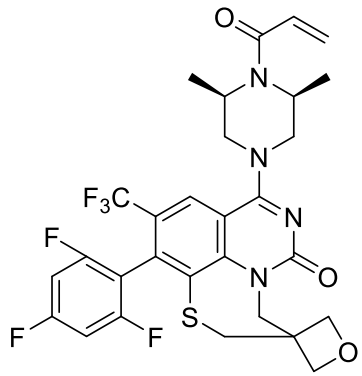
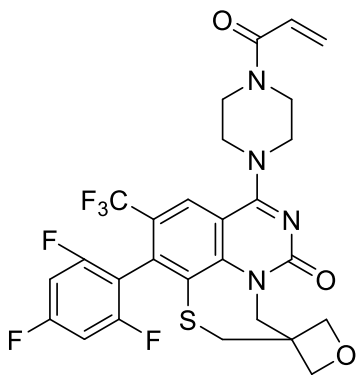
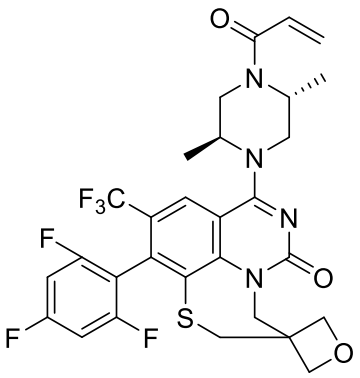
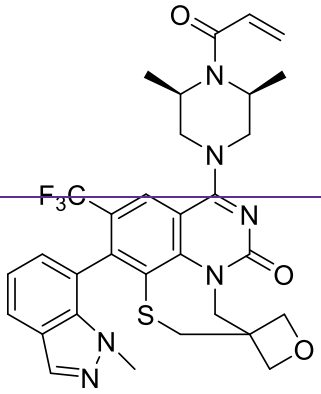
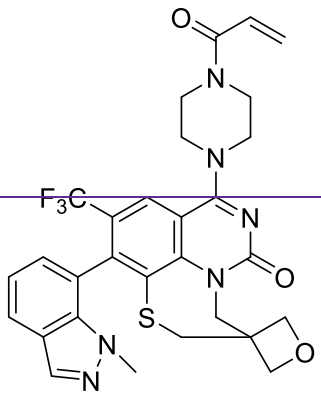
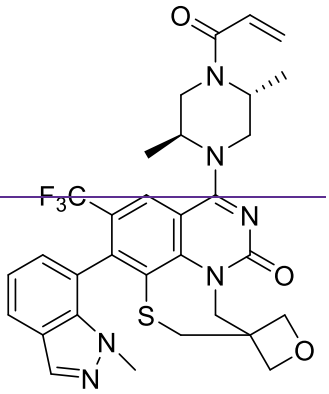
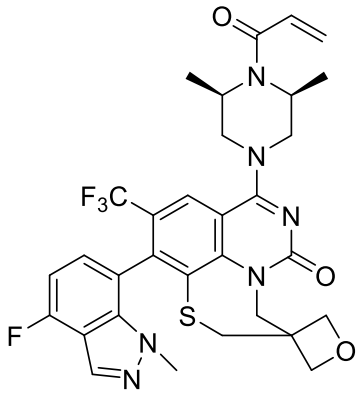
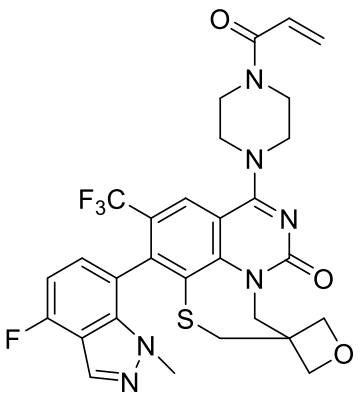
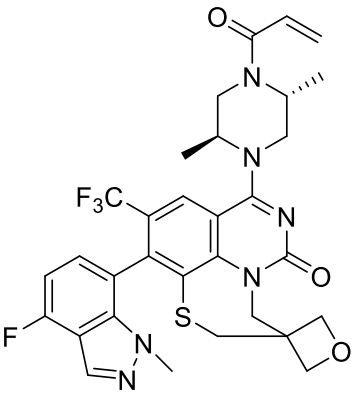


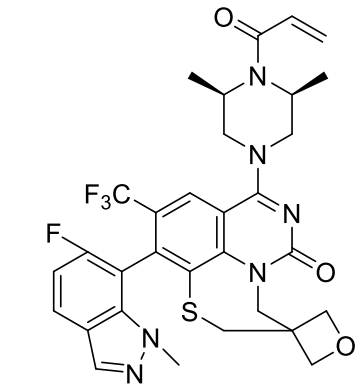
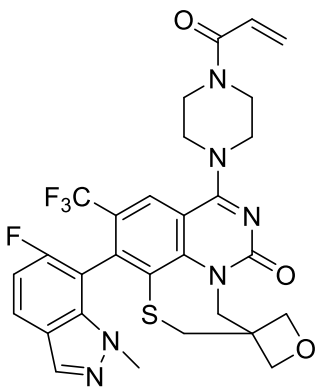
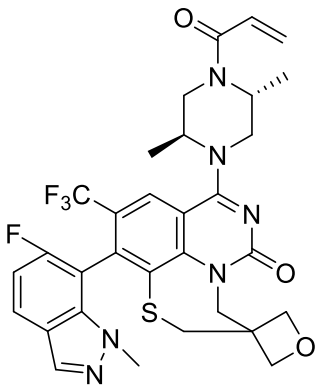
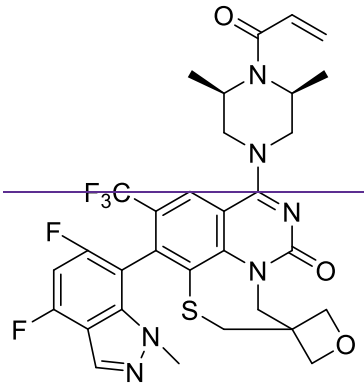
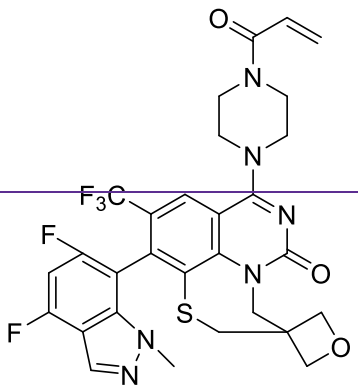
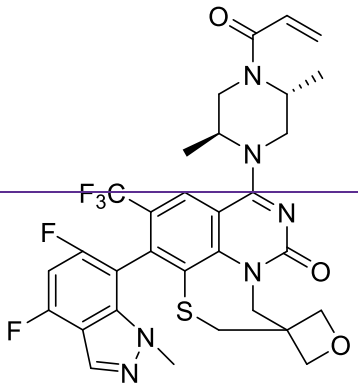
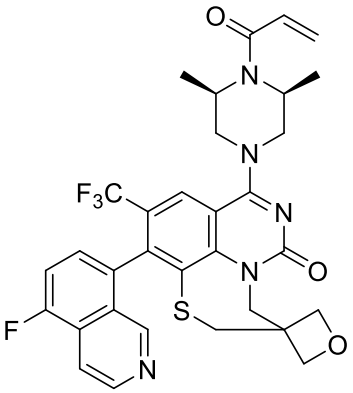
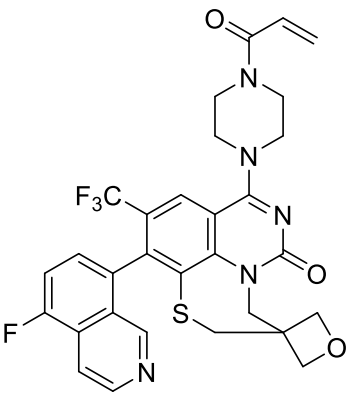
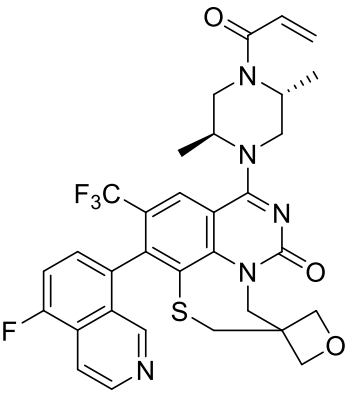


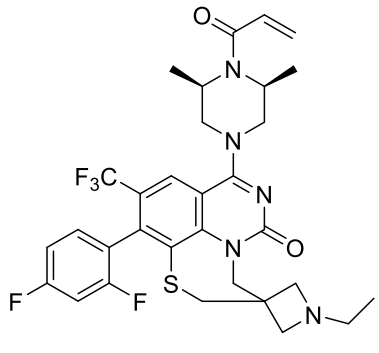
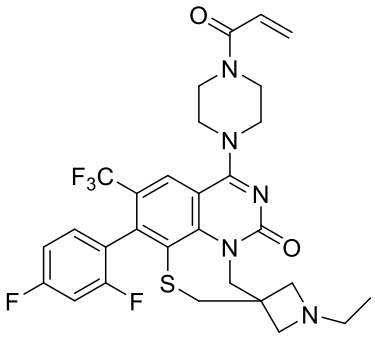
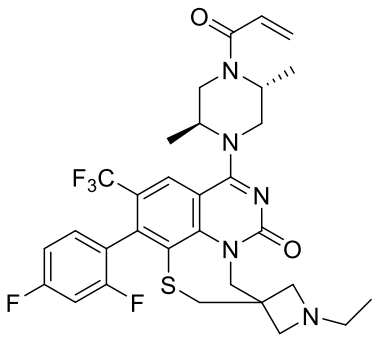
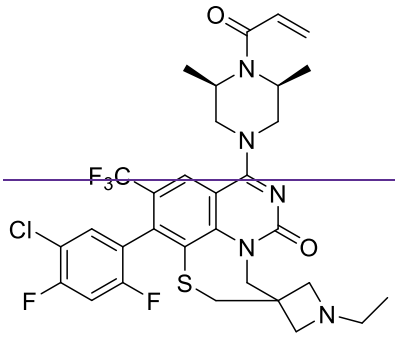
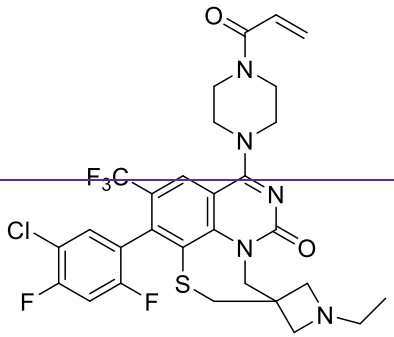
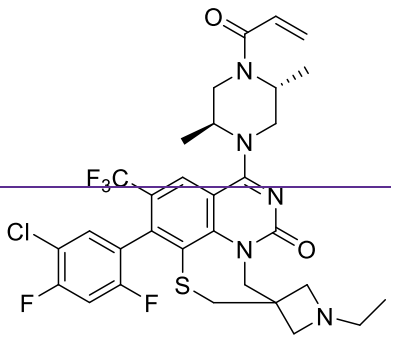
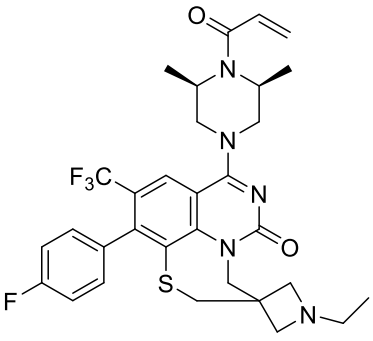
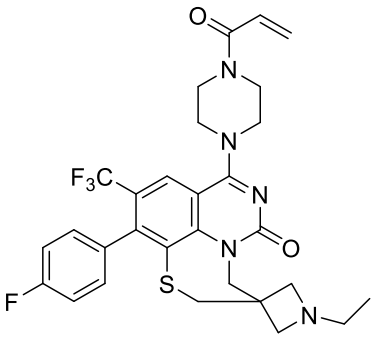
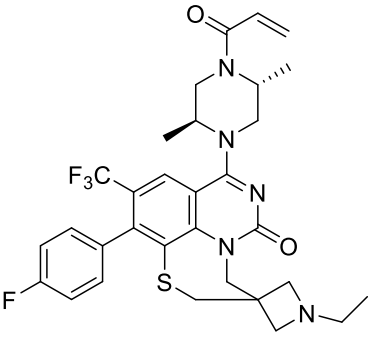


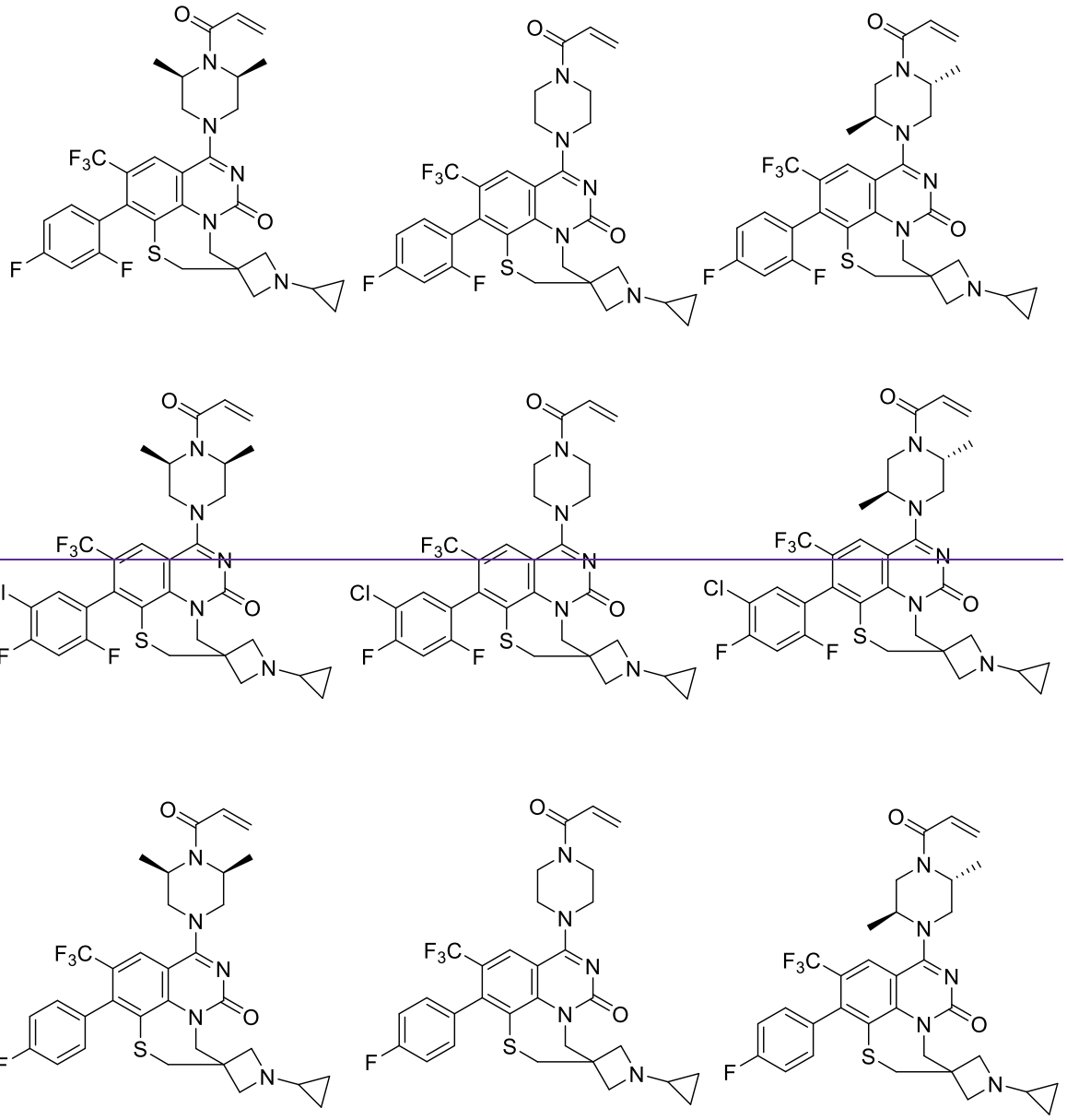


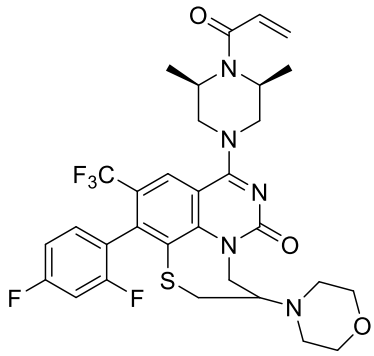
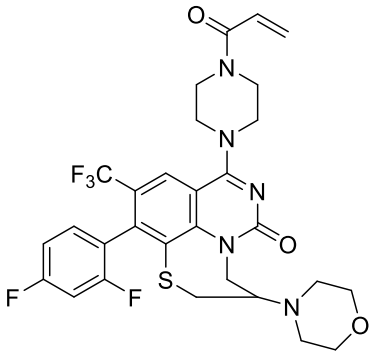
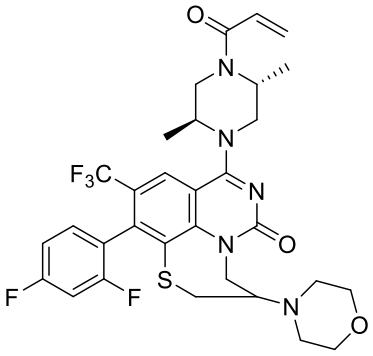
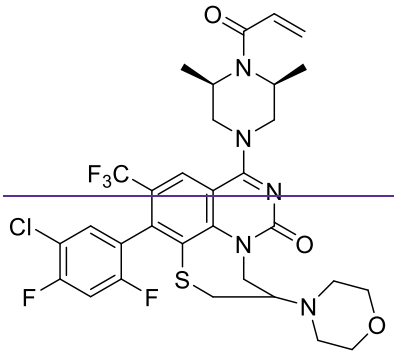
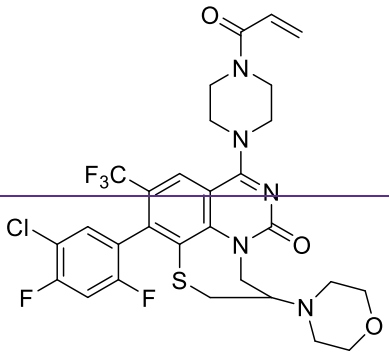
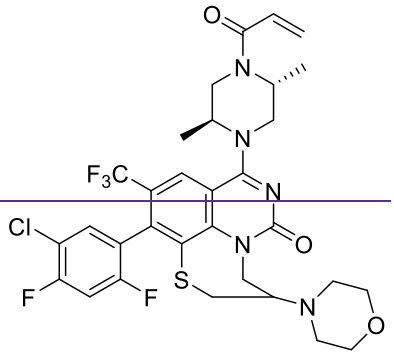
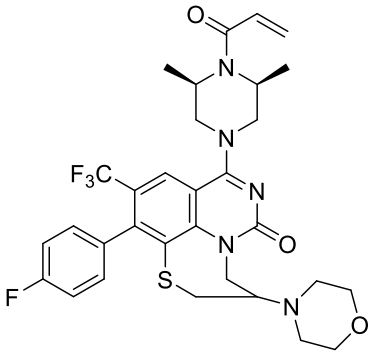
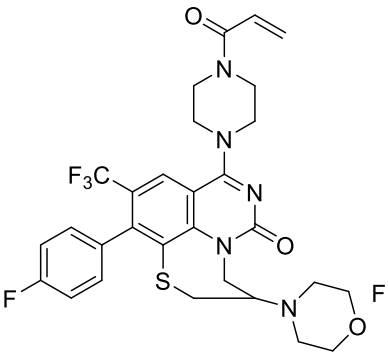
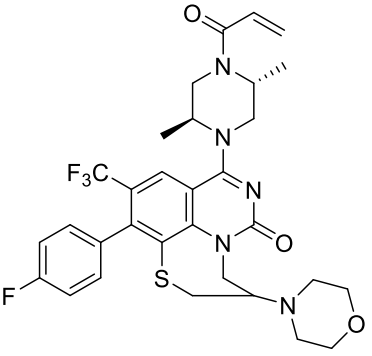


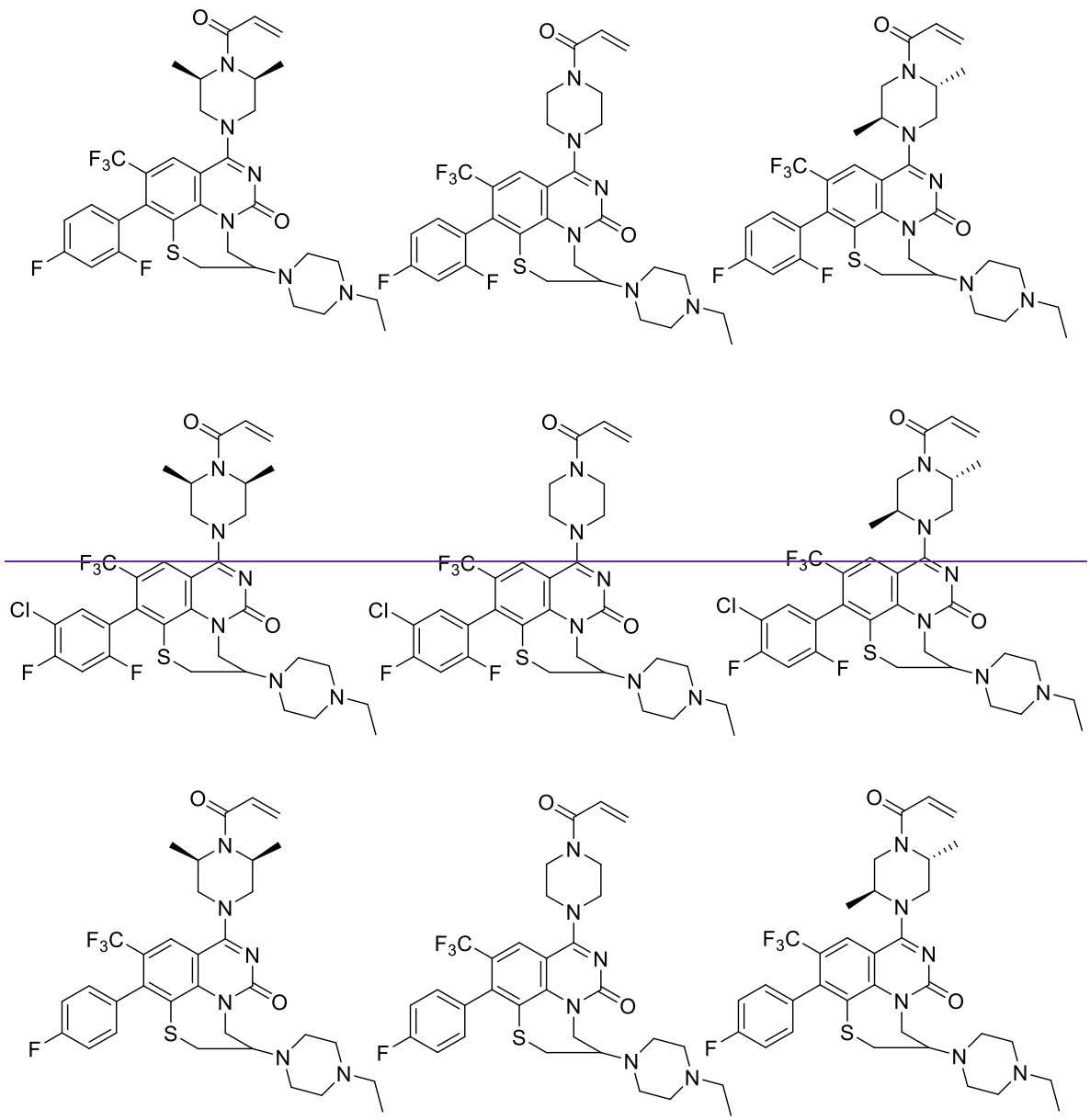










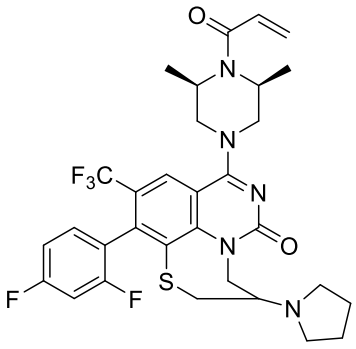
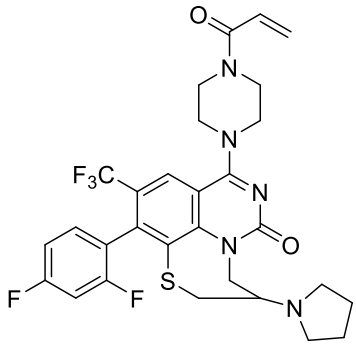
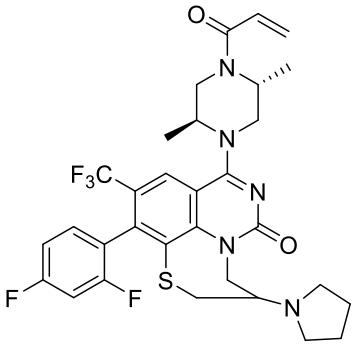
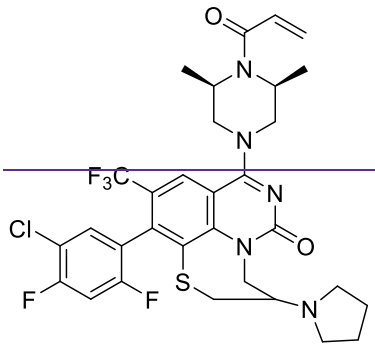
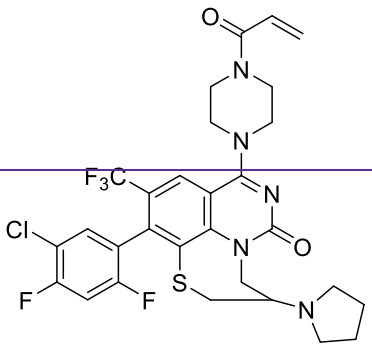
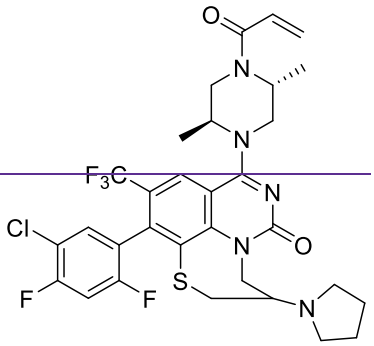
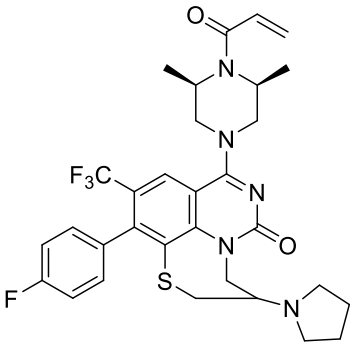
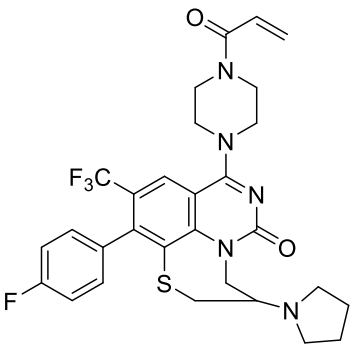
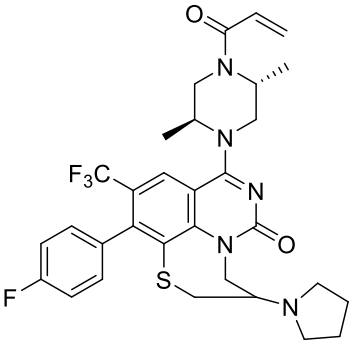










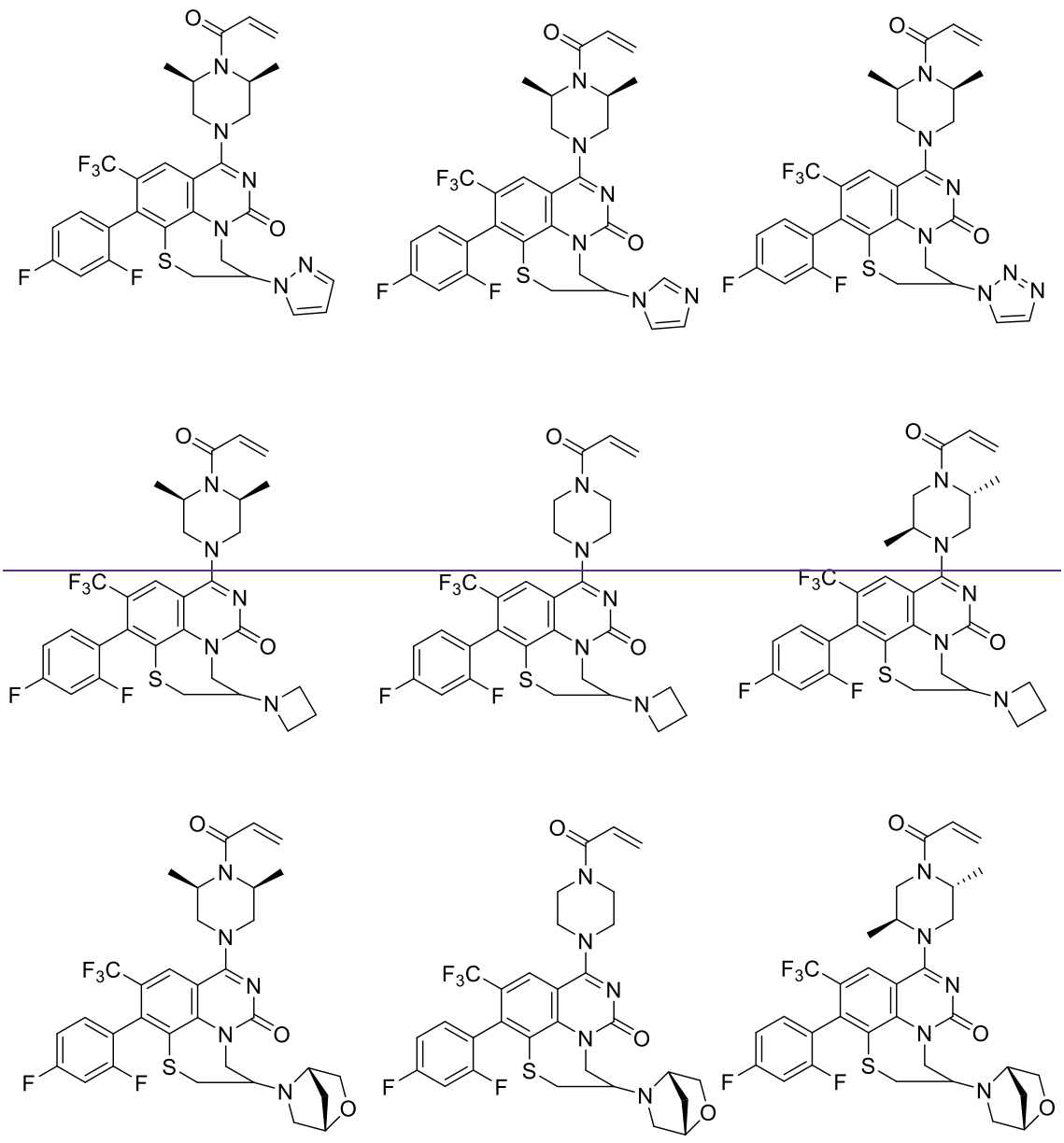










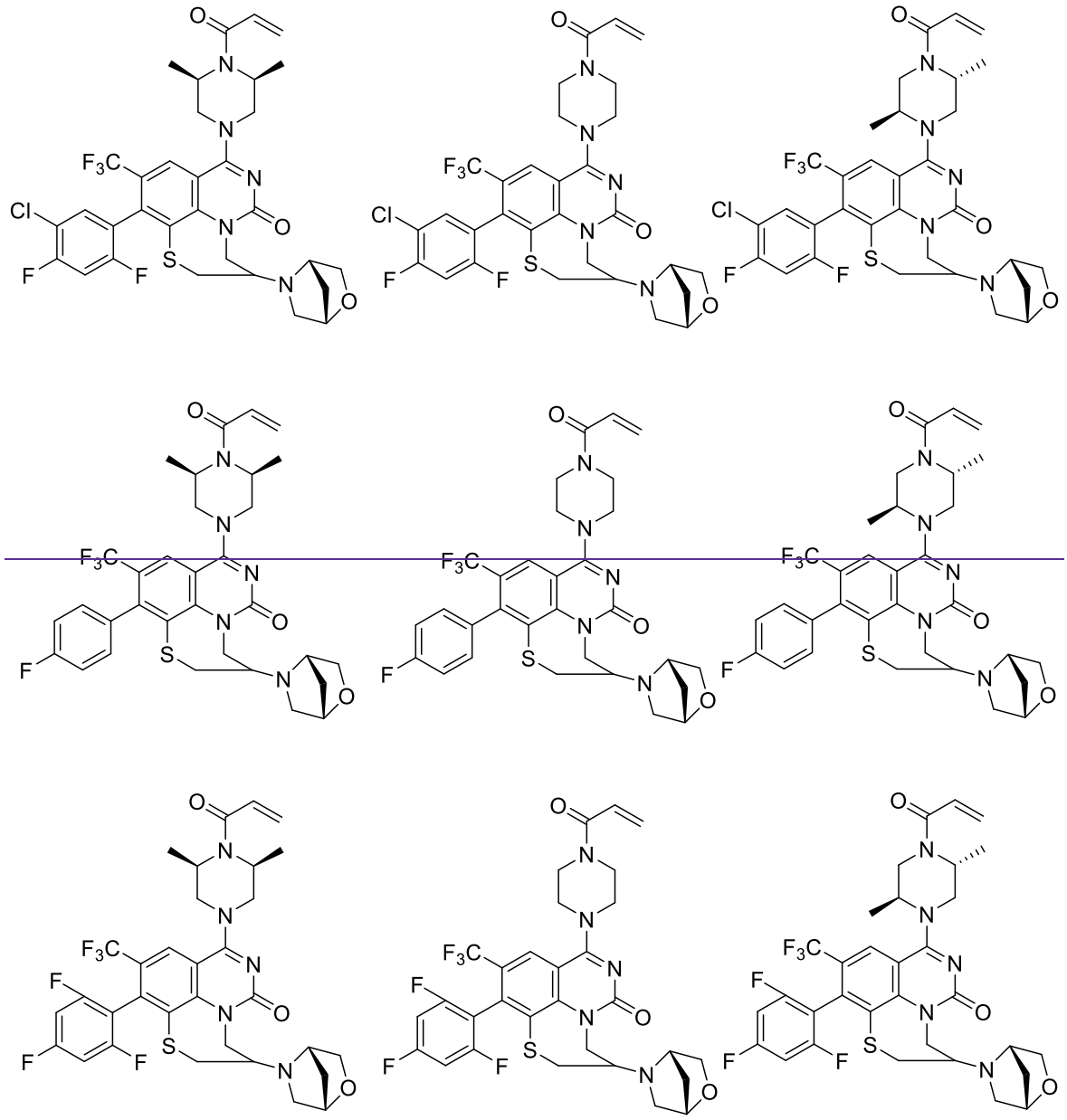


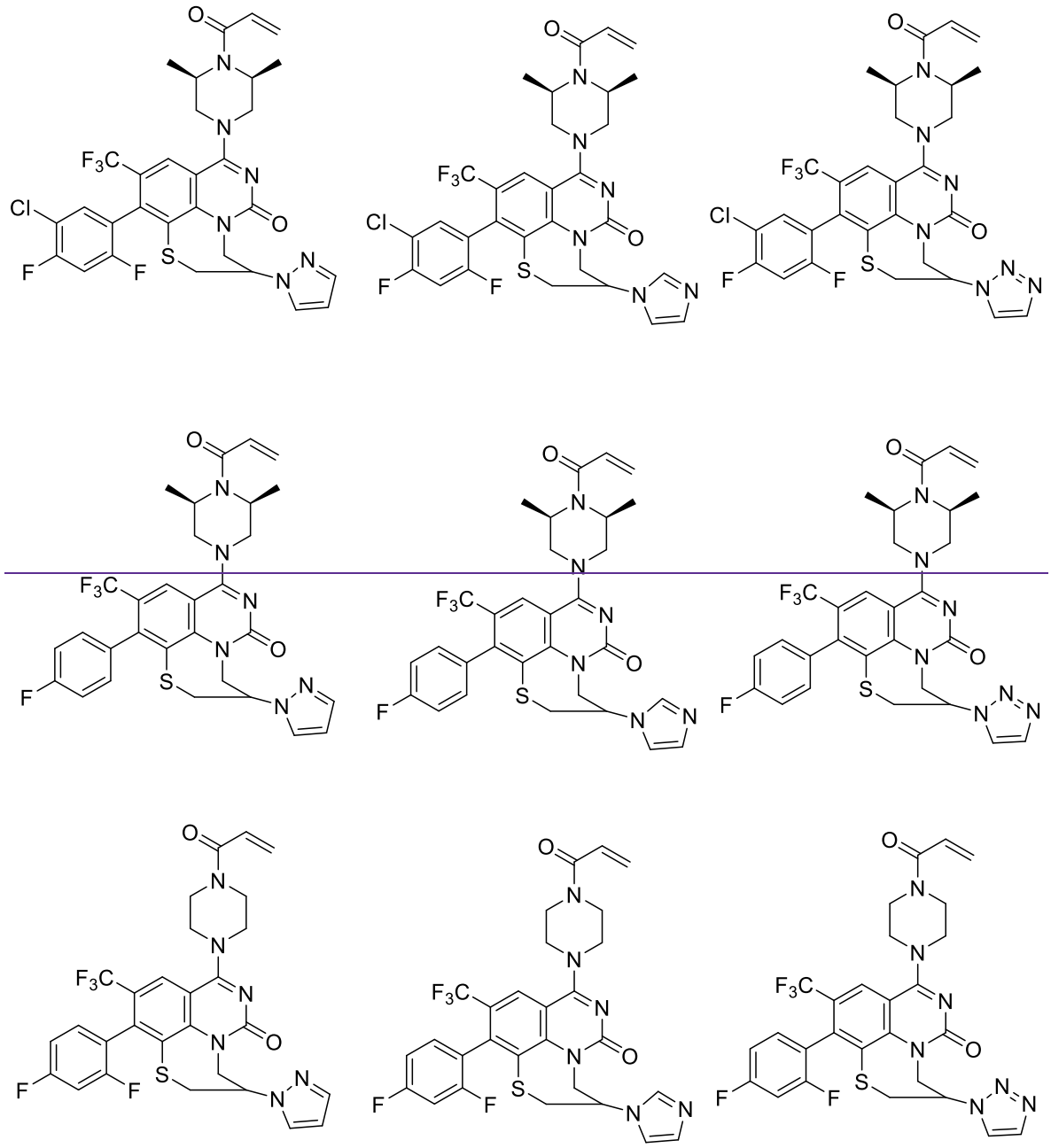


















~~202. A compound selected from Tables 5-7.~~

~~203. A compound selected from Table 8.~~

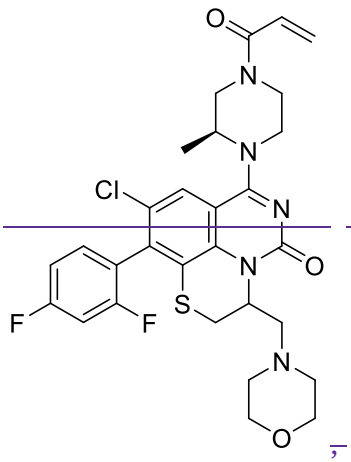
~~204. A pharmaceutical composition comprising a compound of any one of claims 1 to 203.~~

~~205. A method of modulating a G12C mutant K-Ras comprising contacting the G12C mutant K-Ras with a compound of any of claims 1 to 203.~~

~~206. A method of treating a subject with a cancer comprising a K-Ras G12C mutation comprising administering to the subject a compound of any one of claims 1 to 203 or pharmaceutical composition thereof.~~

~~207. Use of a compound of any one of claims 1 to 203 in the manufacture of a medicament for the treatment of a cancer comprising a K-Ras G12C mutation.~~

~~208. The compound of any one of claims 1 to 203, wherein the compound is not:~~



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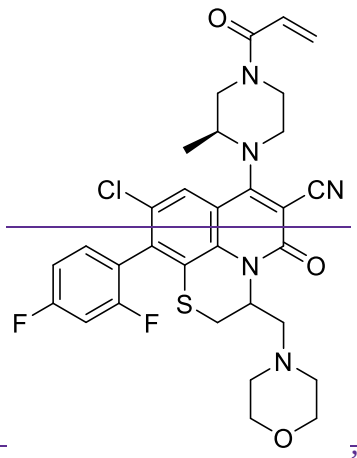

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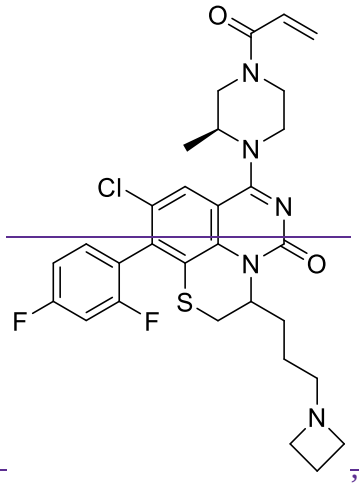

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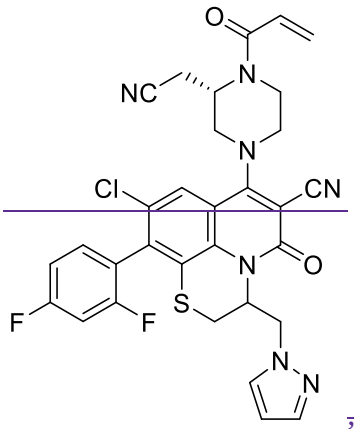

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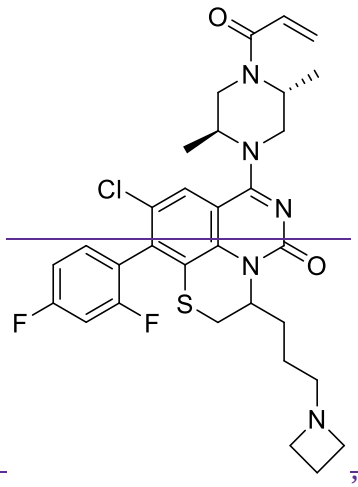

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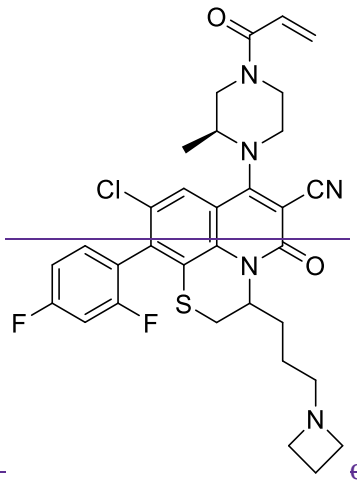
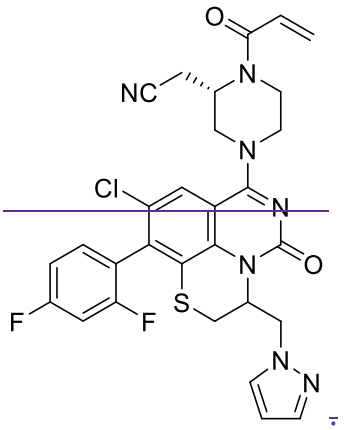


~~or~~



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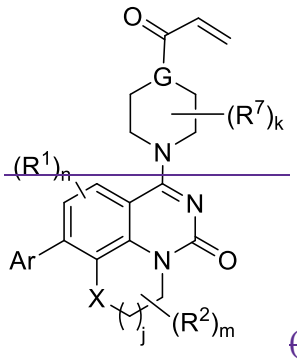
~~209. A compound of Formula (XLVI):~~

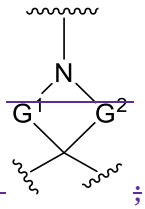


( XLVI)

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;



G is selected from the group consisting of N, CH, and ;

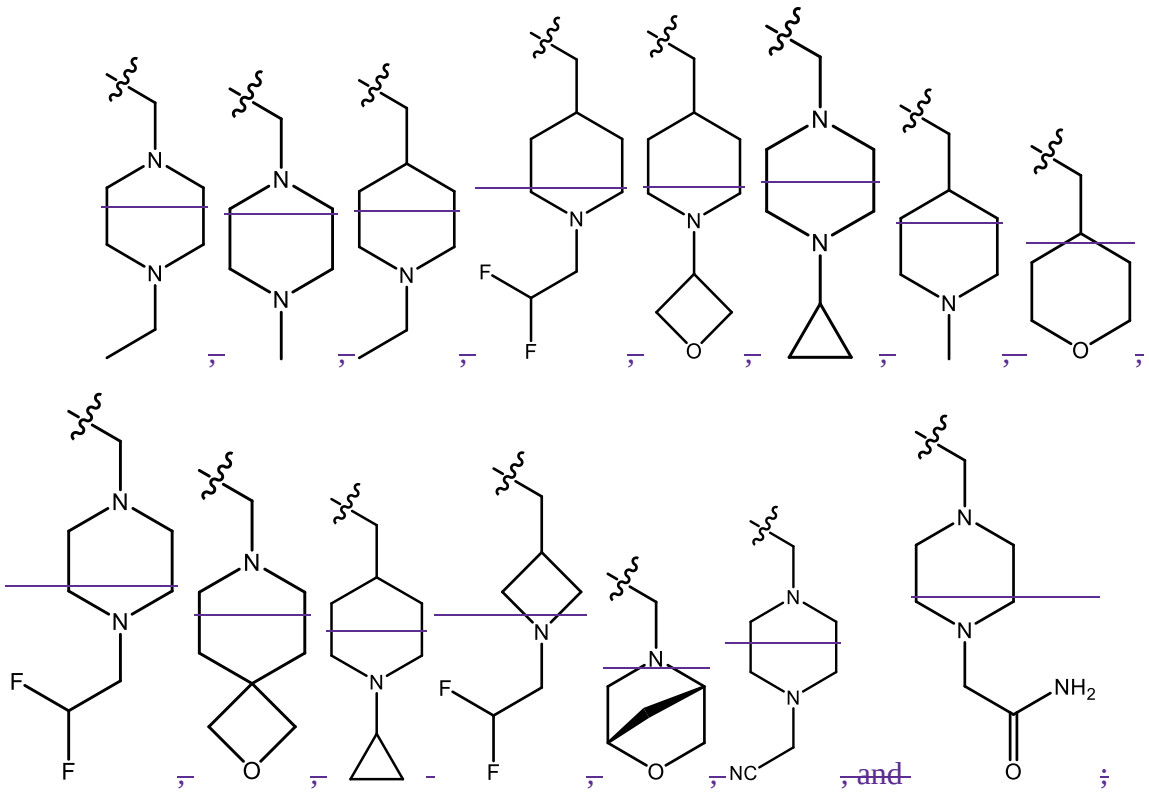
wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

n is an integer from 0 to 2;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted, wherein when j is 1, the heterocyclylalkyl is selected from:



m is an integer from 0 to 6;

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to G is optionally substituted.

210. The compound of claim 209, wherein X is S.

211. The compound of claim 209, wherein X is S=O or $SO_2$.

212. The compound of any one of claims 209 to 234, wherein j is 1.

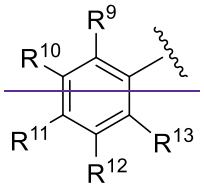
213. The compound of any one of claims 209 to 235, wherein m is 0.

214. The compound of any one of claims 209 to 211, wherein m is 1.

215. The compound of any one of claims 209 to 237, wherein Ar creates axial asymmetry.

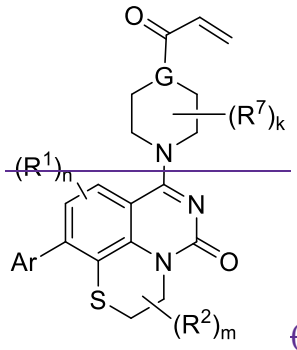
216. The compound of claim 238, where in the compound is a single rotamer.

217. The compound of any one of claims 209 to 239, wherein Ar is:



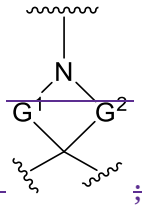
wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

218. A compound of Formula (XLVII):



(XLVII)

wherein:



G is selected from the group consisting of N, CH, and ;

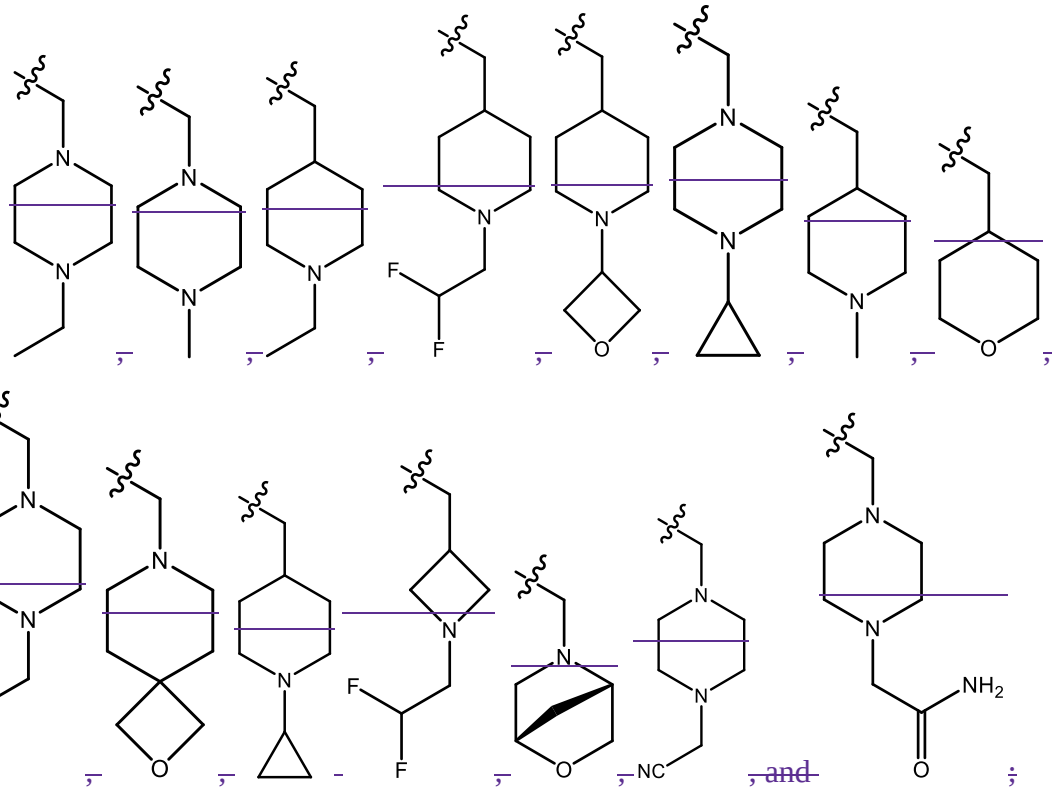
wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

n is an integer from 0 to 2;

$R^2$ is selected from the group consisting of alkyl, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, *N*-alkyl aminoalkyl, *N*,*N*-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted, wherein heterocyclylalkyl is selected from:



m is an integer from 0 to 4;

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to G is optionally substituted.

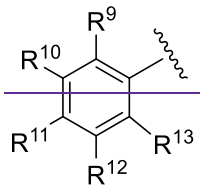
219. The compound of claim 241, wherein m is 0.

220. The compound of claim 241, wherein m is 1.

221. The compound of any one of claims 241 to 243, wherein Ar creates axial asymmetry.

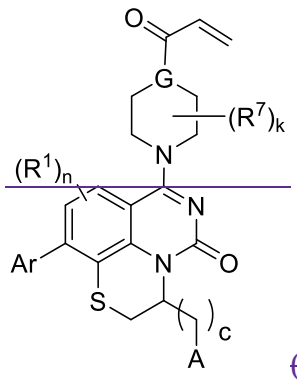
222. The compound of claim 244, wherein the compound is a single rotamer.

223. The compound of any one of claims 241 to 245, wherein Ar is:



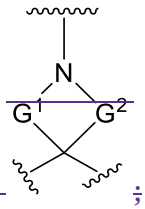
wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

224. A compound of Formula (XLVIII):




(XLVIII)

wherein:

G is selected from the group consisting of N, CH, and 

;

wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

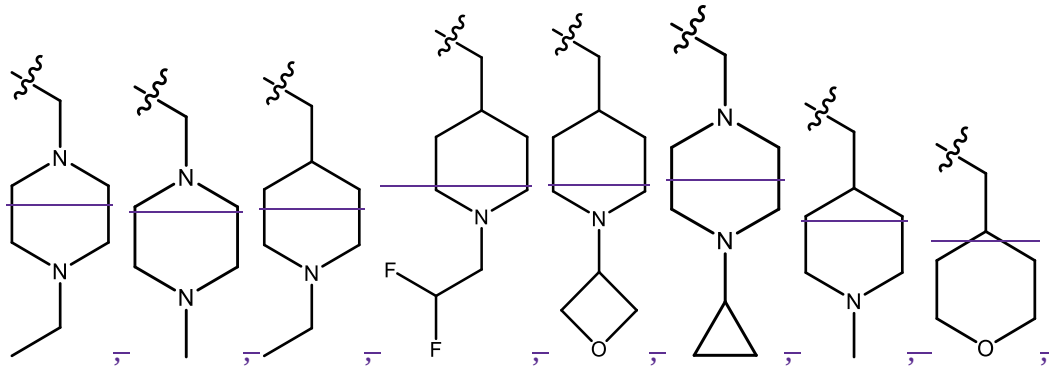
each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

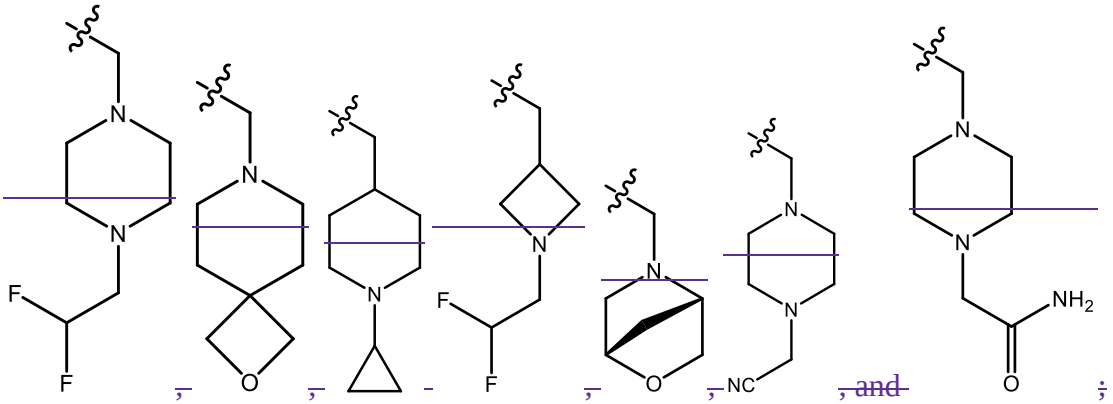
n is an integer from 0 to 2;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted, wherein heterocyclylalkyl is selected from:





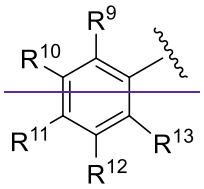
wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to G is optionally substituted.

225. The compound of claim 247, wherein Ar creates axial asymmetry.

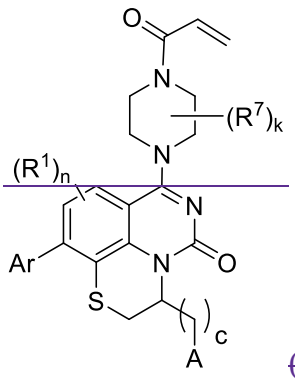
226. The compound of claim 248, wherein the compound is a single rotamer.

227. The compound of any one of claims 247 to 249, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

228. A compound of Formula (XXXIX):



(XXXIV)

wherein:

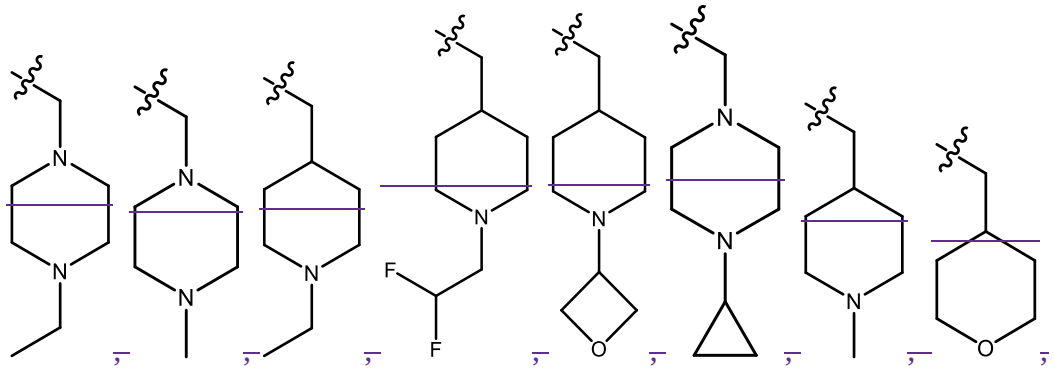
each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

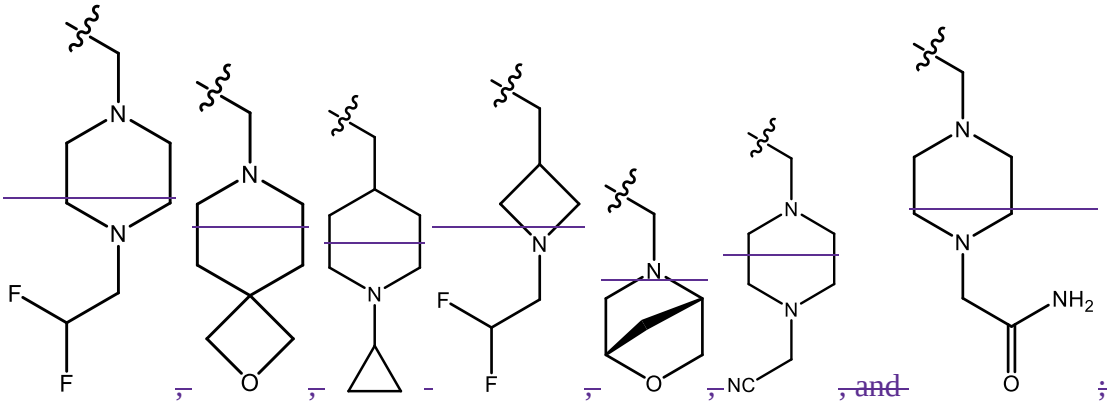
n is an integer from 0 to 2;

Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted, wherein heterocyclylalkyl is selected from:





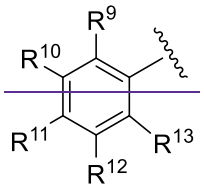
wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to N is optionally substituted.

229. The compound of claim 251, wherein Ar creates axial asymmetry.

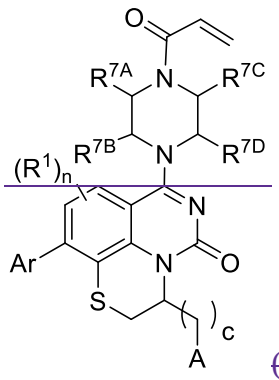
230. The compound of claim 252, wherein the compound is a single rotamer.

231. The compound of any one of claims 251 to 253, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

~~232. A compound of Formula (L):~~




~~(L)~~

~~wherein:~~

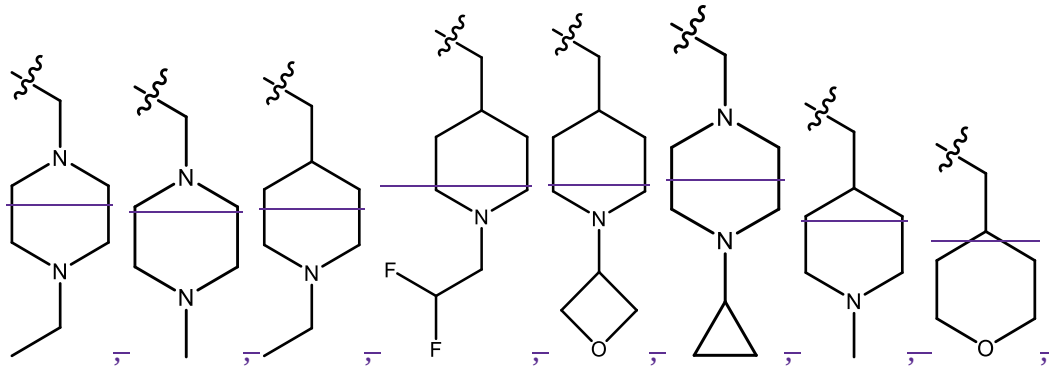
~~each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;~~

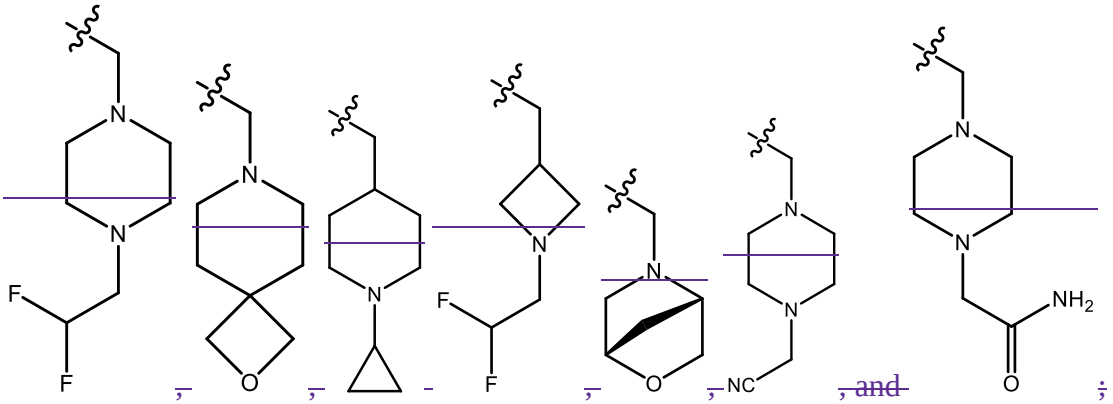
~~n is an integer from 0 to 2;~~

~~Ar is aryl, *N*-arylamino, *N*-aryl-*N*-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, *N*-heteroaryl-*N*-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;~~

~~c is an integer from 0 to 4;~~

~~A is selected from the group consisting of hydroxyl, amino, *N*-alkylamino, *N*,*N*-dialkylamino, cycloalkylamino, *N*-alkylaminoalkyl, *N*,*N*-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted, wherein heterocyclylalkyl is selected from:~~





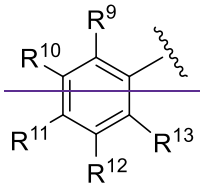
$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, and alkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$.and

wherein the acrylyl moiety linked to N is optionally substituted.

233. The compound of claim 255, wherein Ar creates axial asymmetry.

234. The compound of claim 256, wherein the compound is a single rotamer.

235. The compound of any one of claims 255 to 257, wherein Ar is:



wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted.

236. The compound of any one of claims 255 to 258, wherein $R^{7B}$ is methyl.

237. The compound of claim 259, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *R* configuration.

238. The compound of claim 259, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *S* configuration.

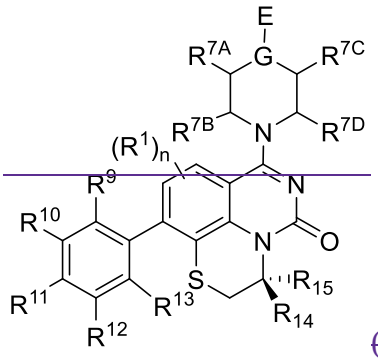
239. The compound of any one of claims 255 to 237, wherein $R^{7C}$ is methyl.

240. The compound of claim 238, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *R* configuration.

241. The compound of claim 238, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *S* configuration.

242. The compound of any one of claims 231 to 264, wherein $R^{7D}$ is hydrogen.

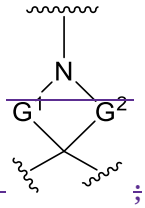
243. A compound of Formula (LI):




(LI)

wherein:

E is an electrophilic moiety;

G is selected from the group consisting of N, CH, and 

;

wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, and alkoxy;

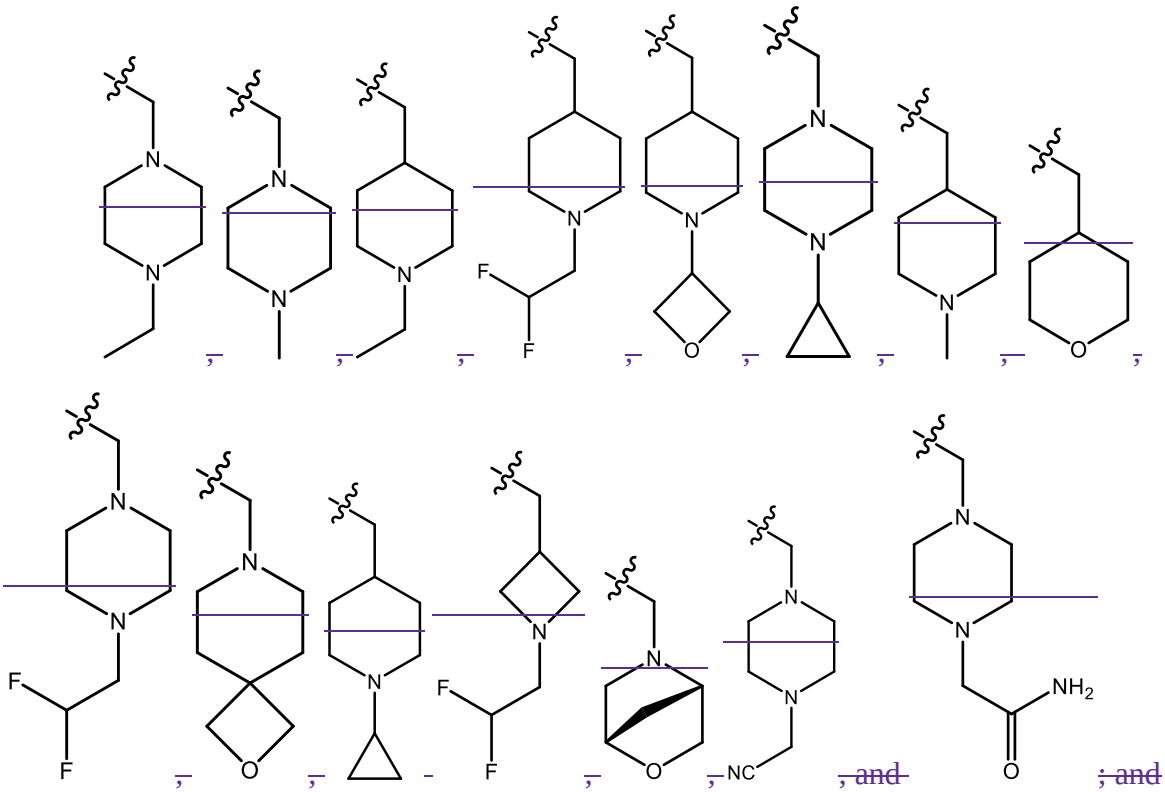
n is an integer from 0 to 2;

$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, and alkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$.

wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any

two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted;

wherein $R^{14}$ and $R^{15}$ are selected from the group consisting of hydrogen, hydroxyl, amino, *N*-alkylamino, dialkylamino, *N*-alkylamino alkyl, *N*,*N*-dialkylamino, *N*,*N*-dialkylamino alkyl, cycloalkylamino, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted, with the proviso that one of $R^{14}$ or $R^{15}$ is hydrogen, wherein heterocyclylalkyl is selected from:



wherein E is optionally substituted.

244. The compound of claim 266, having axial asymmetry.

245. The compound of claim 266 or 267, wherein the compound is a single rotamer.

246. The compound of any one of claims 266 to 268, wherein $R^{7B}$ is methyl.

247. The compound of claim 269, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *R*-configuration.

248. The compound of claim 269, wherein a stereogenic center created by the $R^{7B}$ methyl group is in the *S*-configuration.

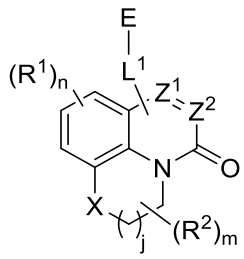
249. The compound of any one of claims 266 to 271, wherein $R^{7C}$ is methyl.

~~250. The compound of claim 272, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *R* configuration.~~

~~251. The compound of claim 272, wherein a stereogenic center created by the $R^{7C}$ methyl group is in the *S* configuration.~~

~~252. The compound of any one of claims 266 to 274, wherein $R^{7D}$ is hydrogen.~~

1. A compound of Formula (XXI) or pharmaceutically acceptable salt thereof:




(XXI);

wherein:

X is $S(O)_p$, wherein p is an integer from 0 to 2;

j is an integer from 0 to 2;

$Z^1$ and $Z^2$ are independently $CR^6$ or N, with the proviso that at least one of $Z^1$ or $Z^2$ is $CR^6$ with $R^6$ being a bond to $L^1$;

$L^1$ is linking group comprising at least one nitrogen atom;

E is an electrophilic moiety, wherein E is bound to $L^1$ via the at least one nitrogen atom;

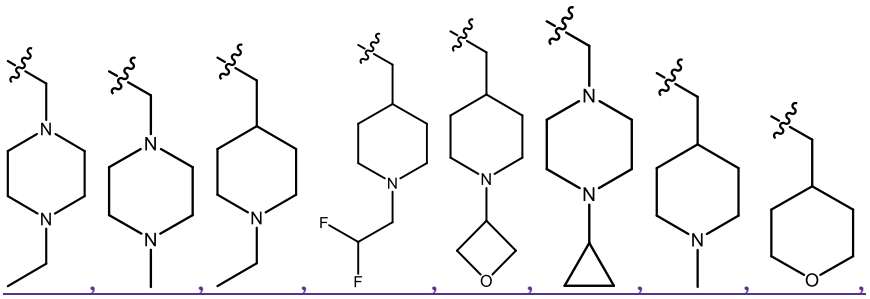
each $R^1$ is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, alkoxy, aryl, heteroaryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, and arylthio with the proviso that:

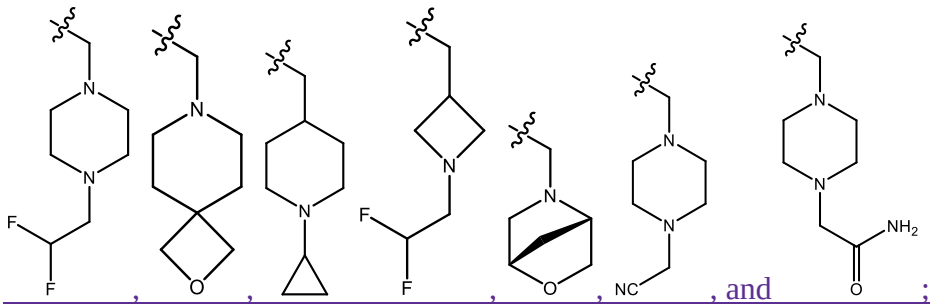
at least one $R^1$ is aryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

n is an integer from 1 to 3;

$R^2$ is selected from the group consisting of alkyl, amino, alkylamino, dialkylamino alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, N-alkyl aminoalkyl, N,N-dialkyl aminoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, cyclopropyloxy, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, hydroxy, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, and oxo any of which are optionally substituted;

wherein when j is 1, the heterocyclylalkyl is selected from:





or two $R^2$ together with the carbon atom to which they are attached form a spirocycle or heterocycle.

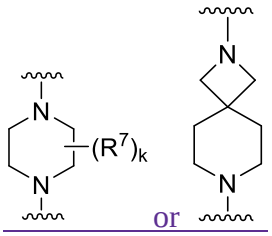
m is an integer from 0 to 6; and

$R^6$ is selected from the group consisting of hydrogen, alkyl, haloakyl, cyano, halo, alkoxy, aryl, heteroaryl, trifluoromethyl and bond to $L^1$.

2. The compound of claim 1, wherein X is S.

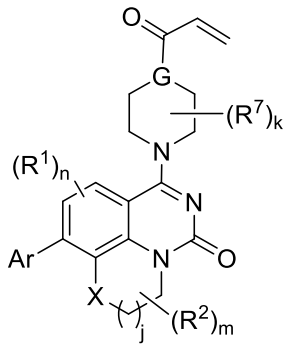
3. The compound of claim 1, wherein m is 0 or 1.

4. The compound of claim 1, wherein $Z^1$ is $CR^6$ with $R^6$ being a bond to $L^1$; wherein $L^1$ is



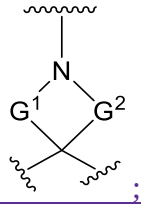
wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl.

5. The compound of claim 1 of Formula (XXIX) or pharmaceutically acceptable salt thereof:



(XXIX)

wherein:

G is selected from the group consisting of N, CH, and  ;

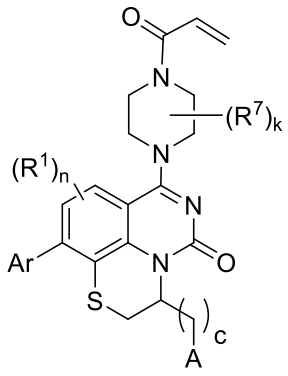
wherein $G^1$ and $G^2$ are independently $(CH_2)_q$, where q is 1 or 2;

Ar is aryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, N-heteroaryl-N-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to G is optionally substituted.

6. The compound of claim 1 of Formula (XXXIV) or pharmaceutically acceptable salt thereof:



(XXXIV)

wherein:

Ar is aryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, N-heteroaryl-N-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted;

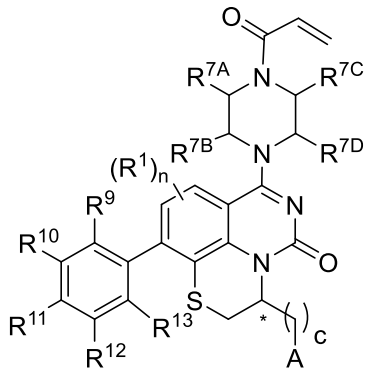
c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted;

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH, $NHR^i$ wherein $R^i$ is hydrogen or alkyl, and cyanomethyl; or any two $R^7$ may combine to form a fused-ring, spiro or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, $SO_2$, or $NR^j$, wherein $R^j$ is H, methyl or trifluoromethyl; and

wherein the acrylyl moiety linked to N is optionally substituted.

7. The compound of claim 1 of Formula (XXXIX) or pharmaceutically acceptable salt thereof:



(XXXIX)

wherein * is a stereogenic center;

$R^{7A}$, $R^{7B}$, $R^{7C}$, and $R^{7D}$ are independently selected from hydrogen, alkyl, and cyanoalkyl; or any two $R^{7A-D}$ may combine to form a fused-ring or bridging bicycle, wherein any one fused-ring or bridging atom is O, S, S=O, or $SO_2$.

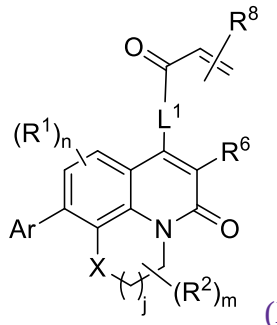
wherein $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ together combine to form a further fused ring that is an aromatic ring optionally comprising 1 to 3 heteroatoms independently selected from N, O or S, the further fused ring being optionally substituted;

c is an integer from 0 to 4;

A is selected from the group consisting of hydroxyl, amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, cycloalkylaminoalkyl, alkylamidoalkyl, arylamidoalkyl, alkylsulfonamidoalkyl, arylsulfonamidoalkyl, alkoxy, alkoxyalkyl, cycloalkyl, alkylcycloalkyl, hydroxyalkyl, halo, haloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, any of which are optionally substituted; and

wherein the acrylyl moiety linked to N is optionally substituted.

8. The compound of claim 1 of Formula (XL) or pharmaceutically acceptable salt thereof:



(XL)

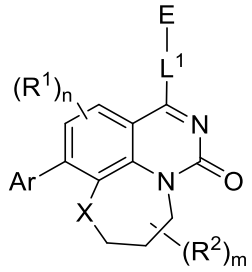
wherein:

$R^6$ is is selected from the group consisting of hydrogen, alkyl, haloakyl, cyano, halo, alkoxy, aryl, heteroaryl, and trifluoromethyl;

$R^8$ is selected from the group consisting of fluorine, methyl, and $-CH_2NR^aR^b$, wherein $R^a$ and $R^b$ are independently selected from hydrogen or alkyl; or $R^a$ and $R^b$ combine to form a $C_2$-$C_6$ nitrogen containing heterocycle; and

Ar is aryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, arylthio, heteroaryl, N-heteroarylamino, N-heteroaryl-N-alkylamino, heteroaryloxy, or heteroarylthio, any of which is optionally substituted.

9. The compound of claim 1 of Formula (XLIII) or pharmaceutically acceptable salt thereof:

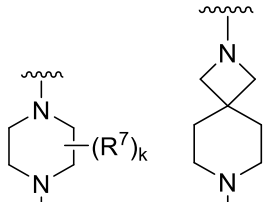



(XLIII)

wherein:

X is S;

$L^1$ is




or

wherein k is an integer from 0 to 4; and each $R^7$ is independently selected from methyl, and cyanomethyl, or any two $R^7$ combine to form a bridge or spirocycle structure optionally comprising a heteroatom in the bridge or spirocycle selected from S, $SO_2$, O or N, and wherein the bridge or spirocycle structure is optionally substituted with oxo;

Ar is selected from the group consisting of aryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

n is an integer from 1 to 2;

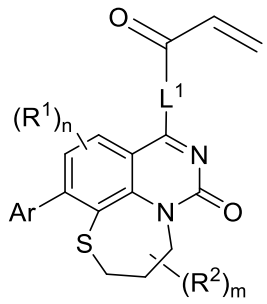
each $R^2$ is independently selected from the group consisting optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CHR'R'', -OR', -SR', and -NR',R''; wherein each R' or R'' is selected from the group consisting of

hydrogen, alkyl, alkoxy, alkoxyalkyl, hydroxy, cycloalkoxy, cyclopropyloxy, cyano, cyanoalkyl, amido, amidoalkyl, N-alkylamido, N-alkylamidoalkyl, N,N-dialkylamido, N,N-dialkylamidoalkyl, amino, aminoalkyl, N-alkyl amino, N-alkyl aminoalkyl, N,N-dialkylamino, and N,N-dialkylaminoalkyl, any of which are optionally substituted; or any two R' and R'' combine to form 3-7-membered ring, optionally comprising 1 or 2 heteroatoms selected from N, O, or S; or any two $R^2$ combine to form a spirocycle comprising 0 to 2 heteroatoms selected from N, O, or S; and

m is an integer from 0 to 2.

10. The compound of claim 9, wherein Ar is a phenyl optionally substituted with one or more alkyl, cycloalkyl, fluoro, chloro, bromo, iodo, trifluoromethyl or cyano.

11. The compound of claim 9 of Formula (XLIV) or pharmaceutically acceptable salt thereof:




(XLIV)

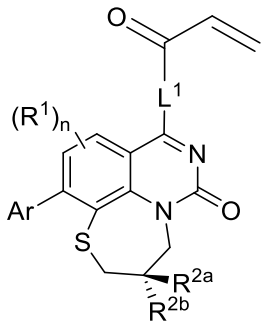
12. The compound of claim 11, wherein n is 1 and $R^1$ is ortho to Ar.

13. The compound of claim 12, wherein $R^1$ is chloro or trifluoromethyl.

14. The compound of claim 11, wherein Ar is a phenyl ring comprising 1 to 3 halogen atoms.

15. The compound of claim 14, wherein Ar is a phenyl ring comprising 1 to 3 fluorine substitutions.

16. The compound of claim 9 of Formula (XLV) or pharmaceutically acceptable salt thereof:



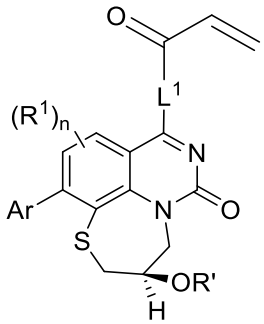
(XLV)

wherein:

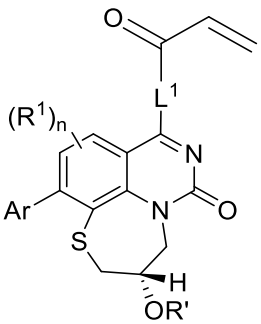
$R^{2a}$ and $R^{2b}$ are independently selected from the group consisting of hydrogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CHR'R'', -OR', -SR', and -NR',R''; wherein each R' or R'' is selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, hydroxy, cycloalkoxy, cyclopropyloxy, cyano, cyanoalkyl, amido, amidoalkyl, N-alkylamido, N-alkylamidoalkyl, N,N-dialkylamido, N,N-dialkylamidoalkyl, amino, aminoalkyl, N-alkyl amino, N-alkyl aminoalkyl, N,N-dialkylamino, N,N-dialkylaminoalkyl, any of which are optionally substituted; or R' and R'' combine to form 3-7-membered ring, optionally comprising 1 or 2 heteroatoms selected from N, O, or S, or $R^{2a}$ and $R^{2b}$ combine to form a spirocycle comprising 0 to 2 heteroatoms selected from N, O, or S; and

Ar is a phenyl optionally substituted with one or more alkyl, cycloalkyl, fluoro, chloro, bromo, iodo, trifluoromethyl or cyano.

17. The compound of claim 11 having the structure of formula XLVa or XLVb :

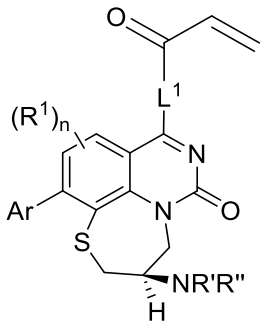


XLVa

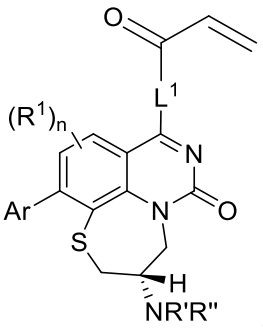


XLVb.

18. The compound of claim 11 having the structure of formula XLVc or XLVd :




XLVc

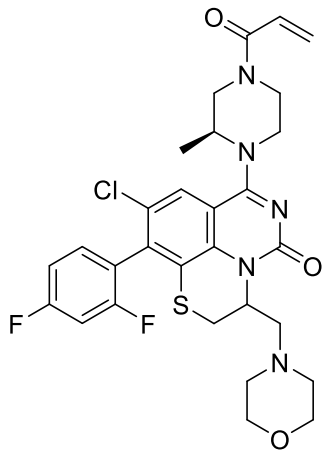



XLVd.

19. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

20. Use of a compound of claim 1 or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer comprising a K-Ras G12C mutation, wherein a G12C mutant K-Ras is to be contacted with the compound of claim 1 to modulate the G12C mutant K-Ras.

21. The compound of claim 1, wherein the compound is not: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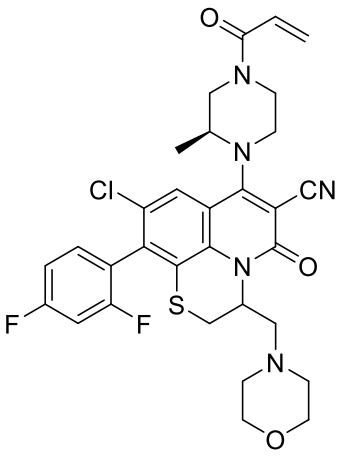
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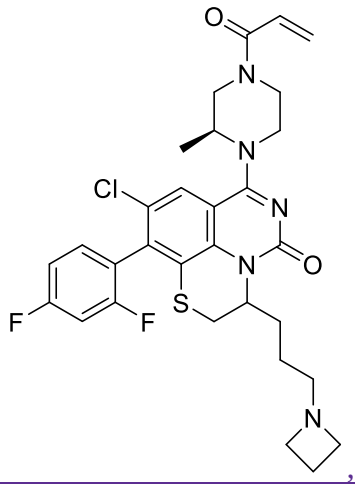
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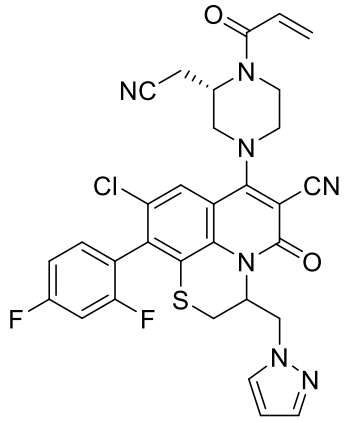
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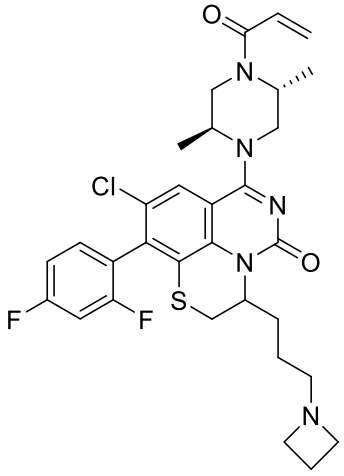
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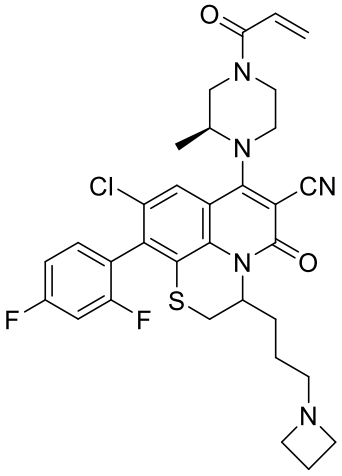
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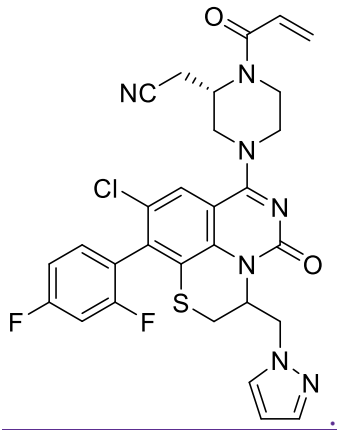
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