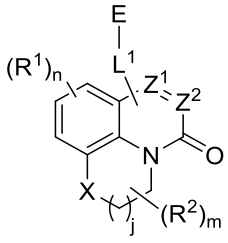
cancer, lung cancers and skin cancers. Finally, N-Ras mutations occur frequently in hepatocellular carcinoma.

[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:

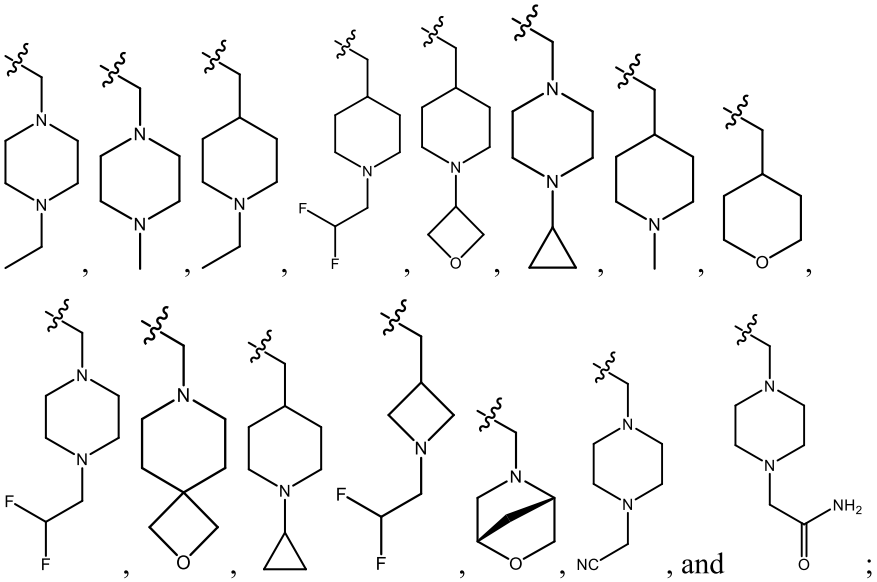
at least one R^1 is aryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, arylthio, or heteroaryl, any of which is optionally substituted;

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.

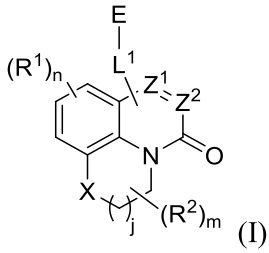
m is an integer from 0 to 6; and

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 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;

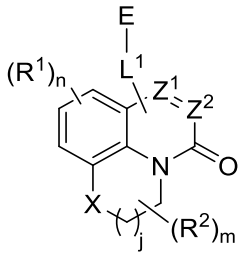
n is an integer from 1 to 3;

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) 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;

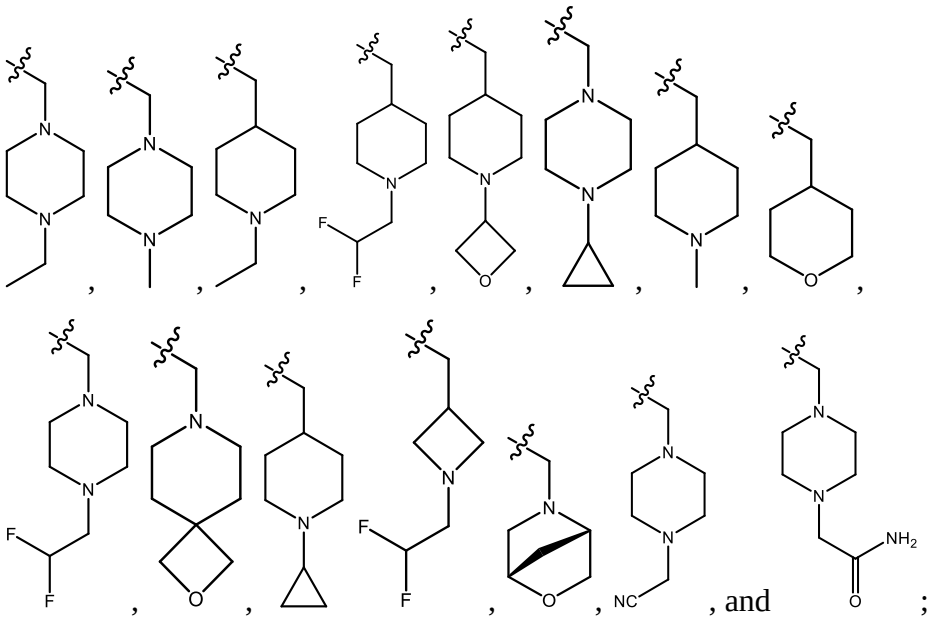
each R^1 is an optional substitution independently selected from the group consisting of alkyl, cyano, cycloalkyl, halo, haloalkyl, trifluoromethyl, alkoxy, aryl, heteroaryl, N-arylamino, N-aryl-N-alkylamino, aryloxy, and arylthio with the proviso that:

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.

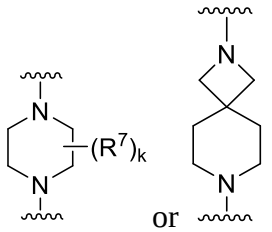
m is an integer from 0 to 6; and

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.

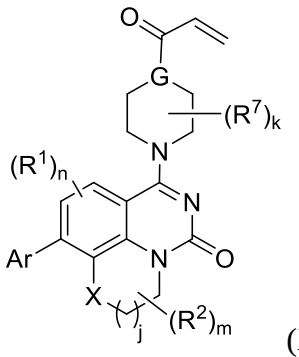
3. The compound of claim 1, wherein m is 0 or 1.

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



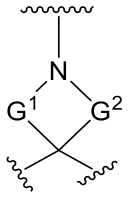
wherein k is an integer from 0 to 4; and each R^7 is independently selected from an alkyl group selected from methyl, ethyl, and propyl, any of which are optionally substituted with one or more fluorine atoms, $-CH_2(CH_3)C=CF_2$, cyano, propargyl, $-CH_2C(O)V$, wherein V is selected from methyl, OH,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

;

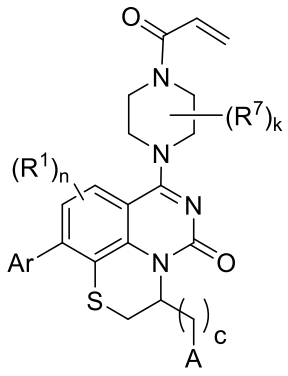
wherein G^1 and G^2 are independently $(CH_2)_q$, where q is 1 or 2;

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;

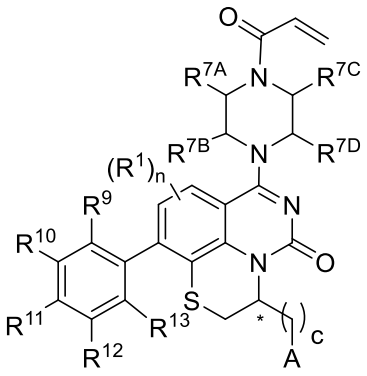
c is an integer from 0 to 4;

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.

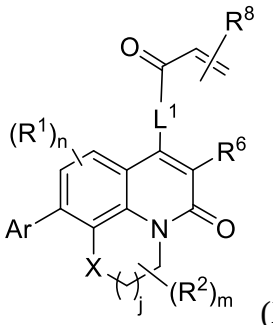
wherein R^9, R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from the group consisiting of hydrogen, halo, alkyl, alkoxy, haloalkyl, trifluoromethyl, cycloalkyl and any two adjacent R^9, R^{10}, R^{11}, R^{12}, and R^{13} together combine to form a further fused ring that is an aromatic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

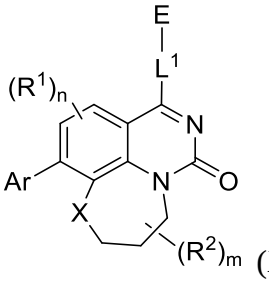
wherein:

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:

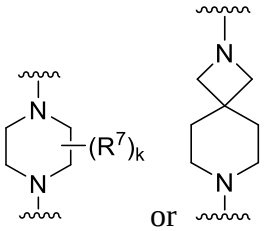


(XLIII)

wherein:

X is S;

L^1 is



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;

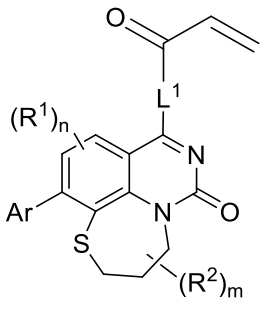
each R^2 is independently selected from the group consisting optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CHR'R'', -OR', -SR', and -NR',R''; wherein each R' or R'' is selected from the group consisting of

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)

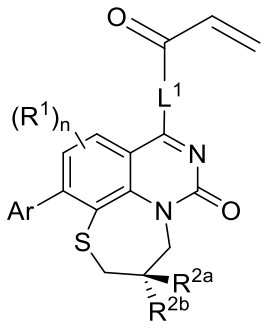
12. The compound of claim 11, wherein n is 1 and R^1 is ortho to Ar.

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:



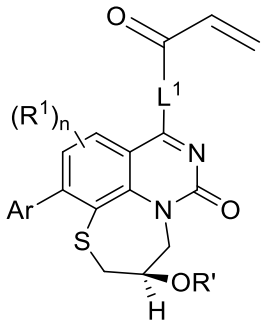
(XLV)

wherein:

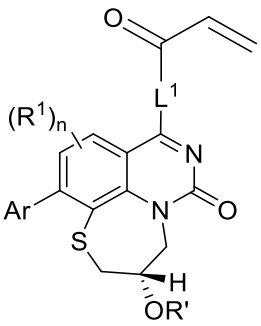
R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -CHR'R'', -OR', -SR', and -NR',R''; wherein each R' or R'' is selected from the group consisting of hydrogen, alkyl, 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 :

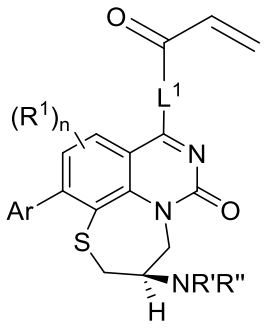


XLVa

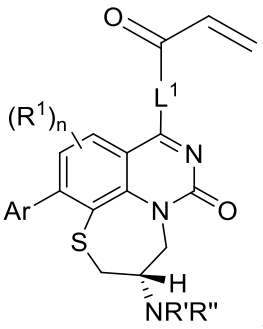


XLVb.

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



XLVc

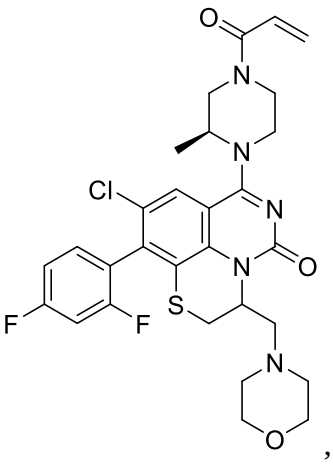
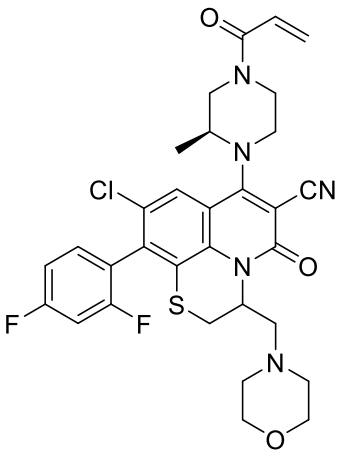
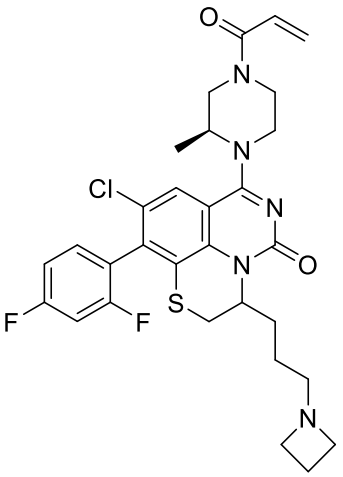
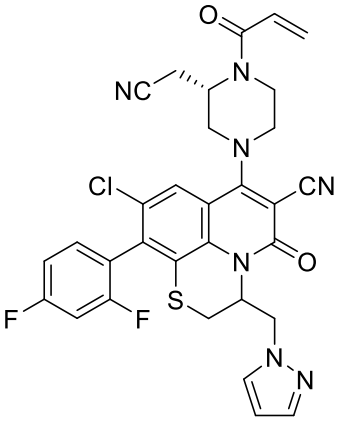
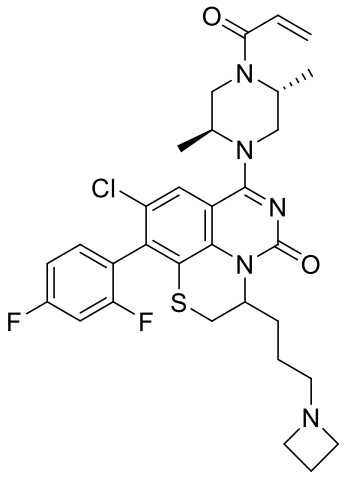
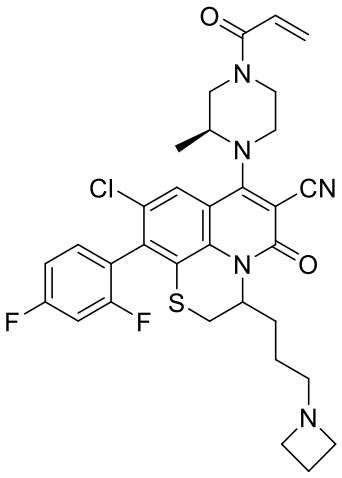
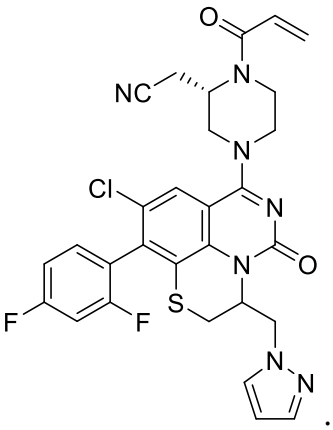


XLVd.

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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or

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