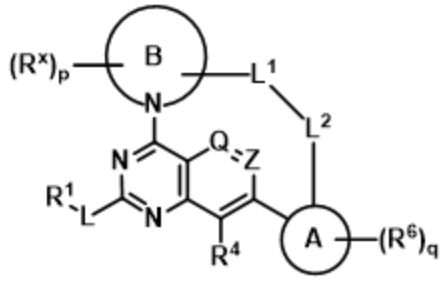
Attempts to develop inhibitors of mutated KRAS proteins have historically been thwarted by the absence of druggable pockets on the surface of the protein (Cox et al., 2014). In 2013, Shokat and colleagues identified covalent inhibitors of a common (O'Bryan, 2019) oncogenic mutant of KRAS, KRAS G12C, which bound to a previously unrecognized allosteric pocket on GDP-KRAS G12C and prevented its subsequent activation (Ostream et al., 2013). This discovery brought about significant new efforts in the KRAS inhibitor research, which have recently culminated in the entry of KRAS inhibitors in human clinical trials.

While some progress has been made on KRAS G12C inhibitors, there is a continued interest and effort to develop inhibitors of KRAS, particularly inhibitors of other KRAS such as KRAS G12D, G12V, G12A, G12S, G13D, Q61H, Q61L or G12C. Thus, there is a need to develop new inhibitors for KRAS G12D, G12V, G12A, G12S, G13D, Q61H, Q61L or G12C for the treatment of disorders, such as cancer.

SUMMARY

In a first example, the present application is directed to compound of formula (**I'**):



(**I'**)

or a pharmaceutically acceptable salt of said compound, wherein;

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a 4-15 membered heterocycloalkyl having 0-3 additional ring heteroatoms independently selected from O, S and N;

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;

each R^x is independently hydroxyl, halogen, oxo, cyano, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkyl, 5-7 membered heteroaryl, -$S(O)_2$-C_{1-}

$_4$alkyl, -$S(O)_2N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, -$C(O)N(R^z)_2$, -C_{1-4} alkylene-$C(O)$-C_{1-4}alkyl, -C_{1-4} alkylene-$C(O)N(R^z)_2$, C_{1-4} alkylene-$S(O)_2$-C_{1-4}alkyl, or -S-C_{1-4}alkyl;

L is a bond, C_{1-6} alkylene, -O-C_{1-6} alkylene, -S-C_{1-6} alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, -O-C_{1-6} alkylene and -S-C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2;

-L^1-L^2- is -L^2, -$N(R^z)C(O)$-L^2, -$C(O)$-L^2-, -$OC(O)$-L^2, -$C(O)O$-L^2, -$OC(O)$-O-L^2, -$OC(S)$-O-L^2, -O-L^2, -$N(R^z)C(O)O$-L^2, -$OC(O)N(R^z)$-L^2, -$N(R^z)$-L^2, -$S(O)_2$-L^2, -S-L^2, -$S(O)$-L^2, C_{1-4} alkylene-$C(O)$-L^2, C_{1-4} alkylene-$C(O)O$-L^2, -C_{1-4} alkylene-$OC(O)O$-L^2, -C_{1-4} alkylene-$OC(O)$-L^2, -C_{1-4} alkylene-O-L^2, -C_{1-4} alkylene-$S(O)_2$-L^2, -C_{1-4} alkylene-S-L^2, -C_{1-4} alkylene-$S(O)$-L^2, -O-5-6 membered heteroaryl-L^2, -C_{1-4} alkylene-5-6 membered heteroaryl-L^2, -C_{1-4} hydroxyalkylene-5-6-membered heteroaryl-L^2 or a 5-6 membered heteroaryl-L^2;

L^2 is C_{1-6} alkylene, C_{1-6} alkylene-O-, C_{1-6} alkylene-O-C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-7} cycloalkylene, C_{1-4} alkylene-C_{3-7} cycloalkylene, C_{1-4} haloalkylene-C_{3-7} cycloalkylene, C_{3-7} cycloalkylene-C_{1-4} alkylene, C_{1-6} hydroxyalkylene or C_{1-6} haloalkylene;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

R^2 is halogen, hydroxyl, C_{1-4} alkyl or two R^2 on the same or adjacent carbon atoms can be taken together to form a C_{3-7} cycloalkyl;

A is C_{6-10} aryl or 5-10 membered heteroaryl and is substituted with q occurrences of R^6;

R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or -O-C_{2-4} alkynyl;

each R^6 independently is halogen, hydroxyl, cyano, -$N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or two R^6 taken together on adjacent carbon atoms form a C_{3-7} cycloalkyl;

T is C_{1-4} alkylene, -$S(O)_2$-, -$C(O)$-, -C_{1-4} alkylene-$C(O)$-, C_{1-4} alkylene-$S(O)_2$- or -S-;

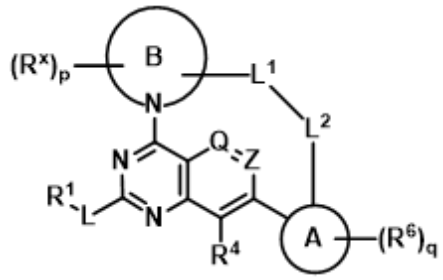
R^y is C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or -$N(R^z)_2$; and

each R^z is hydrogen or C_{1-4} alkyl.

In a second example, provided herein is a pharmaceutical composition comprising a compound described herein or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable excipient.

In a third example, provided herein is a compound described herein, or a pharmaceutically acceptable salt of said compound, or the pharmaceutical composition as described herein for use in treating cancer (e.g., non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma).

In one aspect, the present disclosure refers to a compound of Formula (I'):



(**I'**)

or a pharmaceutically acceptable salt of said compound, wherein;

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a 4-15 membered heterocycloalkyl having 0-3 additional ring heteroatoms independently selected from O, S and N;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

each R^x is independently hydroxyl, halogen, oxo, cyano, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkyl, 5-7 membered heteroaryl, -$S(O)_2$-C_{1-4}alkyl, -$S(O)_2N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, -$C(O)N(R^z)_2$, -C_{1-4} alkylene-C(O)-C_{1-4}alkyl, -C_{1-4} alkylene-$C(O)N(R^z)_2$, C_{1-4} alkylene-$S(O)_2$-C_{1-4}alkyl, or -S-C_{1-4}alkyl;

L is a bond, C_{1-6} alkylene, -O-C_{1-6} alkylene, -S-C_{1-6} alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, -O-C_{1-6} alkylene and -S-C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2;

$-L^1-L^2-$ is $-L^2$, $-N(R^z)C(O)-L^2$, $-C(O)-L^2-$, $-OC(O)-L^2$, $-C(O)O-L^2$, $-OC(O)-O-L^2$, $-OC(S)-O-L^2$, $-O-L^2$, $-N(R^z)C(O)O-L^2$, $-OC(O)N(R^z)-L^2$, $-N(R^z)-L^2$, $-S(O)_2-L^2$, $-S-L^2$, $-S(O)-L^2$, C_{1-4} alkylene-$C(O)-L^2$, C_{1-4} alkylene-$C(O)O-L^2$, $-C_{1-4}$ alkylene-$OC(O)O-L^2$, $-C_{1-4}$ alkylene-$OC(O)-L^2$, $-C_{1-4}$ alkylene-$O-L^2$, $-C_{1-4}$ alkylene-$S(O)_2-L^2$, $-C_{1-4}$ alkylene-$S-L^2$, $-C_{1-4}$ alkylene-$S(O)-L^2$, -O-5-6 membered heteroaryl-L^2, $-C_{1-4}$ alkylene-5-6 membered heteroaryl-L^2, $-C_{1-4}$ hydroxyalkylene-5-6-membered heteroaryl-L^2 or a 5-6 membered heteroaryl-L^2;

L^2 is C_{1-6} alkylene, C_{1-6} alkylene-O-, C_{1-6} alkylene-O-C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-7} cycloalkylene, C_{1-4} alkylene-C_{3-7} cycloalkylene, C_{1-4} haloalkylene-C_{3-7} cycloalkylene, C_{3-7} cycloalkylene-C_{1-4} alkylene, C_{1-6} hydroxyalkylene or C_{1-6} haloalkylene;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

R^2 is halogen, hydroxyl, C_{1-4} alkyl or two R^2 on the same or adjacent carbon atoms can be taken together to form a C_{3-7} cycloalkyl;

A is C_{6-10} aryl or 5-10 membered heteroaryl and is substituted with q occurrences of R^6;

R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, $-T-R^y$, hydroxyl, $-N(R^z)_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or $-O-C_{2-4}$ alkynyl;

each R^6 independently is halogen, hydroxyl, cyano, $-N(R^z)_2$, $-C(O)R^z$, $-C(O)OR^z$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or two R^6 taken together on adjacent carbon atoms form a C_{3-7} cycloalkyl;

T is C_{1-4} alkylene, $-S(O)_2-$, $-C(O)-$, $-C_{1-4}$ alkylene-$C(O)-$, C_{1-4} alkylene-$S(O)_2-$ or $-S-$;

R^y is halogen, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or $-N(R^z)_2$; and

each R^z is hydrogen or C_{1-4} alkyl.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound or salt as described herein and a pharmaceutically acceptable excipient.

In one aspect, the present disclosure refers to a compound or salt as described herein or the pharmaceutical composition as described herein for use as a medicament.

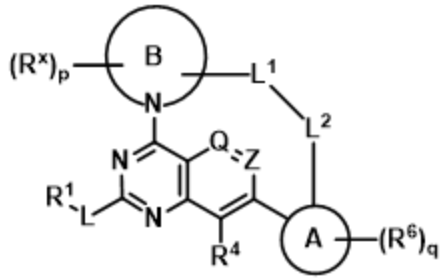
In one aspect, the present disclosure refers to the use of the compound or salt as described herein or the pharmaceutical composition as described herein in the preparation of a medicament for treating cancer.

In one aspect, the present disclosure refers to the use of the compound or salt according to any one of claims 1-61 or the pharmaceutical composition according to claim 62 in the preparation of a medicament for treating cancer, wherein one or more cells of the cancer express a KRAS G12D mutant protein.

Reference will now be made in detail to examples of the present disclosure. While certain examples of the present disclosure will be described, it will be understood that it is not intended to limit the examples of the present disclosure to those described examples. To the contrary, reference to examples of the present disclosure is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the examples of the present disclosure as defined by the appended claims.

DETAILED DESCRIPTION

Provided herein as embodiment 1 is a compound of formula (**I'**):



(**I'**)

or a pharmaceutically acceptable salt of said compound, wherein;

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

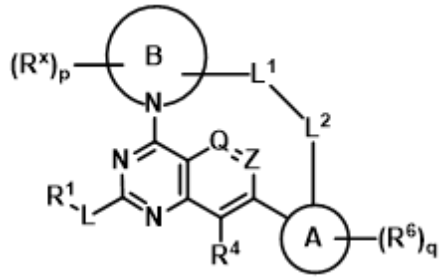
B is a 4-15 membered heterocycloalkyl having 0-3 additional ring heteroatoms independently selected from O, S and N;

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;

What is claimed is:

1. A compound of Formula (**I'**):



(**I'**)

or a pharmaceutically acceptable salt of said compound, wherein;

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a 4-15 membered heterocycloalkyl having 0-3 additional ring heteroatoms independently selected from O, S and N;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

each R^x is independently hydroxyl, halogen, oxo, cyano, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkyl, 5-7 membered heteroaryl, -$S(O)_2$-C_{1-4}alkyl, -$S(O)_2N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, -$C(O)N(R^z)_2$, -C_{1-4} alkylene-C(O)-C_{1-4}alkyl, -C_{1-4} alkylene-$C(O)N(R^z)_2$, C_{1-4} alkylene-$S(O)_2$-C_{1-4}alkyl, or -S-C_{1-4}alkyl;

L is a bond, C_{1-6} alkylene, -O-C_{1-6} alkylene, -S-C_{1-6} alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, -O-C_{1-6} alkylene and -S-C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2;

-L^1-L^2- is -L^2, -$N(R^z)C(O)$-L^2, -C(O)-L^2-, -OC(O)-L^2, -C(O)O-L^2, -OC(O)-O-L^2, -OC(S)-O-L^2, -O-L^2, -$N(R^z)C(O)O$-L^2, -OC(O)$N(R^z)$-L^2, -$N(R^z)$-L^2, -$S(O)_2$-L^2, -S-L^2, -S(O)-L^2, C_{1-4} alkylene-C(O)-L^2, C_{1-4} alkylene-C(O)O-L^2, -C_{1-4} alkylene-OC(O)O-L^2, -C_{1-4} alkylene-OC(O)-L^2, -C_{1-4} alkylene-O-L^2, -C_{1-4} alkylene-$S(O)_2$-L^2, -C_{1-4} alkylene-S-L^2, -C_{1-4} alkylene-S(O)-L^2, -O-5-6 membered heteroaryl-L^2, -C_{1-4} alkylene-5-6 membered heteroaryl-L^2, -C_{1-4} hydroxyalkylene-5-6-membered heteroaryl-L^2 or a 5-6 membered heteroaryl-L^2;

L^2 is C_{1-6} alkylene, C_{1-6} alkylene-O-, C_{1-6} alkylene-O-C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-7} cycloalkylene, C_{1-4} alkylene-C_{3-7} cycloalkylene, C_{1-4} haloalkylene-C_{3-7} cycloalkylene, C_{3-7} cycloalkylene-C_{1-4} alkylene, C_{1-6} hydroxyalkylene or C_{1-6} haloalkylene;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

R^2 is halogen, hydroxyl, C_{1-4} alkyl or two R^2 on the same or adjacent carbon atoms can be taken together to form a C_{3-7} cycloalkyl;

A is C_{6-10} aryl or 5-10 membered heteroaryl and is substituted with q occurrences of R^6;

R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or -O-C_{2-4} alkynyl;

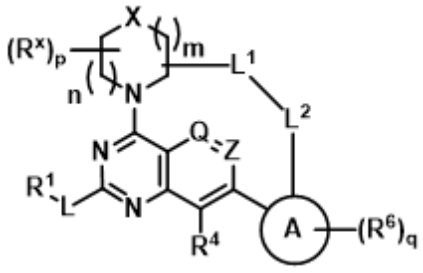
each R^6 independently is halogen, hydroxyl, cyano, -$N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or two R^6 taken together on adjacent carbon atoms form a C_{3-7} cycloalkyl;

T is C_{1-4} alkylene, -$S(O)_2$-, -C(O)-, -C_{1-4} alkylene-C(O)-, C_{1-4} alkylene-$S(O)_2$- or -S-;

R^y is halogen, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or -$N(R^z)_2$; and

each R^z is hydrogen or C_{1-4} alkyl.

2. The compound or salt of claim 1, wherein the compound is a compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt of said compound, wherein;

X is N, CH_2, O, S, S(O), S(O)(NR^z) or $S(O)_2$;

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

n is 0, 1, 2, or 3;

m is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

each R^x is hydroxyl, halogen, oxo, cyano, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, 5-7 membered heteroaryl, -T-R^y or two R^x taken together with the same carbon or adjacent carbon atoms can form C_{3-7} cycloalkyl, a 3-7 membered heterocycloalkyl, wherein each C_{3-7} cycloalkyl or 3-7 membered heterocycloalkyl is further substituted with 0-3 occurrences of R^y or two R^x taken together can form a bridged ring where the bridge is selected from one of the following: -C_{1-4} alkylene, -C_{1-4} alkylene-O-C_{1-4} alkylene-, -O-, -S- or -C_{1-4} alkylene-S-C_{1-4} alkylene- and wherein each C_{1-4} alkylene is further substituted with 0-2 occurrences of R^y;

L is a bond, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylene, -O-C_{1-6} alkylene, -S-C_{1-6} alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, -O-C_{1-6} alkylene and -S-C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2;

-L^1-L^2- is -L^2, -$N(R^z)$C(O)-L^2, -C(O)-L^2-, -OC(O)-L^2, -C(O)O-L^2, -OC(O)-O-L^2, -OC(S)-O-L^2, -O-L^2, -$N(R^z)$C(O)O-L^2, -OC(O)$N(R^z)$-L^2, -$N(R^z)$-L^2, -$S(O)_2$-L^2, -S-L^2, -S(O)-L^2, C_{1-4} alkylene-C(O)-L^2, C_{1-4} alkylene-C(O)O-L^2, -C_{1-4} alkylene-OC(O)O-L^2, -C_{1-4} alkylene-OC(O)-L^2, -C_{1-4} alkylene-O-L^2, -C_{1-4} alkylene-$S(O)_2$-L^2, -C_{1-4} alkylene-S-L^2, -C_{1-4} alkylene-S(O)-L^2, -O-5-6 membered heteroaryl-L^2, -C_{1-4} alkylene-5-6 membered heteroaryl-L^2, -C_{1-4} hydroxyalkylene-5-6-membered heteroaryl-L^2 or a 5-6 membered heteroaryl-L^2;

L^2 is C_{1-6} alkylene, C_{1-6} alkylene-O-, C_{1-6} alkylene-O-C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-7} cycloalkylene, C_{1-4} alkylene-C_{3-7} cycloalkylene, C_{1-4} haloalkylene-C_{3-7} cycloalkylene, C_{3-7} cycloalkylene-C_{1-4} alkylene, C_{1-6} hydroxyalkylene or C_{1-6} haloalkylene;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

R^2 is halogen, hydroxyl, C_{1-4} alkyl or two R^2 on the same or adjacent carbon atoms can be taken together to form a C_{3-7} cycloalkyl;

A is C_{6-10} aryl or 5-10 membered heteroaryl and is substituted with q occurrences of R^6;

R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or -O-C_{2-4} alkynyl;

each R^6 independently is halogen, hydroxyl, cyano, -$N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or two R^6 taken together on adjacent carbon atoms form a C_{3-7} cycloalkyl;

T is C_{1-4} alkylene, -$S(O)_2$-, -C(O)-, -C_{1-4} alkylene-C(O)-, C_{1-4} alkylene-$S(O)_2$- or -S-;

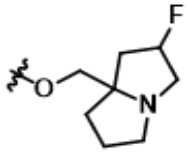
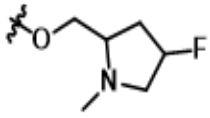
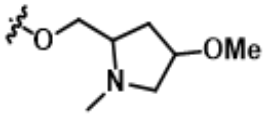
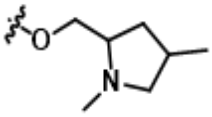
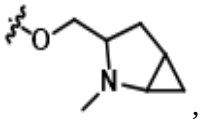
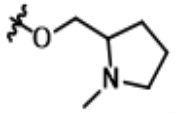
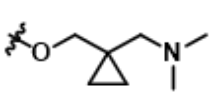
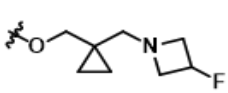
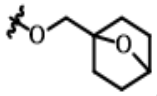
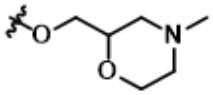
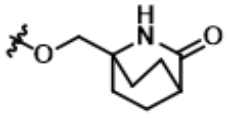
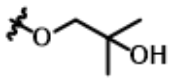
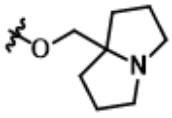
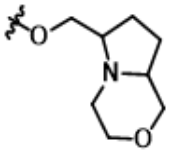
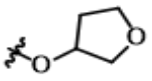
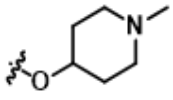
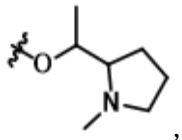
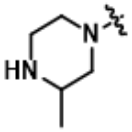
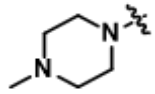
R^y is halogen, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or -$N(R^z)_2$; and

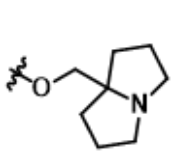
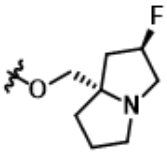
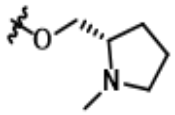
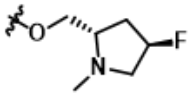
each R^z is hydrogen or C_{1-4} alkyl.

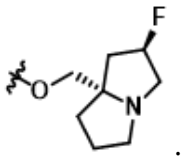
3. The compound or salt of claim 2, wherein Z is N and Q is CH or Z is C-F and Q is CH.

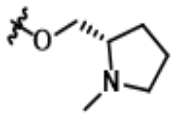
4. The compound or salt of claim 2, wherein L is -O-methylene-, -O-ethylene-, -O-*n*-propylene or -O-isopentanylene and L is substituted with 0-2 occurrences of R^2.

5. The compound or salt according to claim 2, wherein -L-R^1 is

, , , , , , , , , , , , , , , , , , , methoxy or methyl.

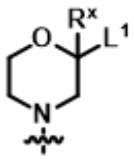
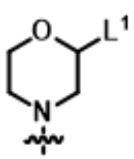
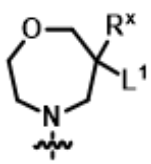
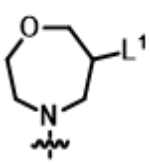
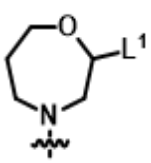
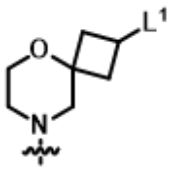
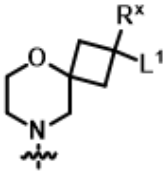
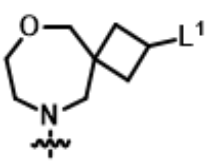
6. The compound or salt of claim 5, wherein -L-R^1 is  ,  ,  or  .

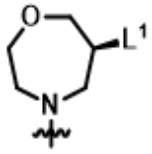
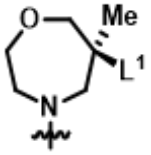
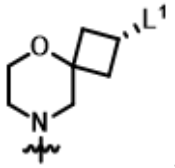
7. The compound or salt of claim 6, wherein -L-R^1 is  .

8. The compound or salt of claim 6, wherein -L-R^1 is  .

9. The compound or salt of any one of claims 2-8, wherein n is 1 and m is 1 or n is 1 and m is 2 or n is 2 and m is 1.

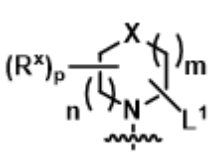
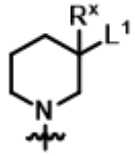
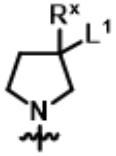
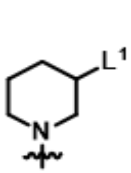
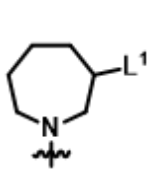
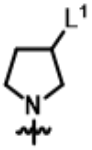
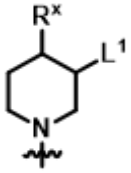
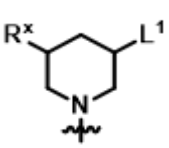
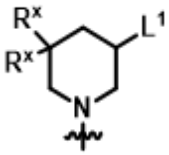
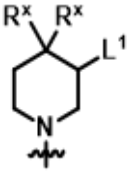
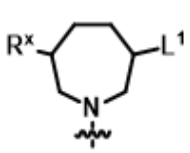
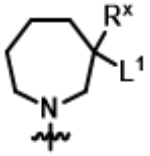
10. The compound or salt of claim 9, wherein X is O.

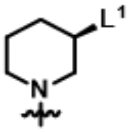
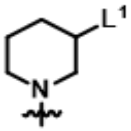
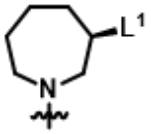
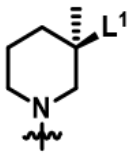
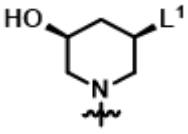
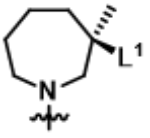
11. The compound or salt of any one of claims 1-10, wherein B-L^1 is  ,  ,  ,  ,  ,  ,  or  .

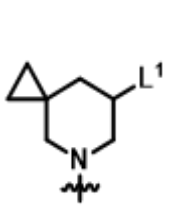
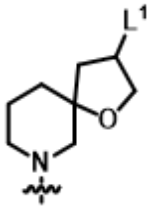
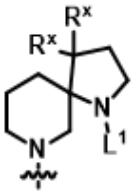
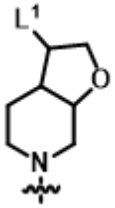
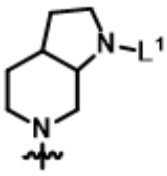
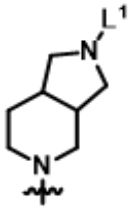
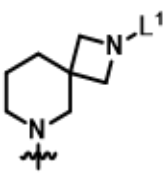
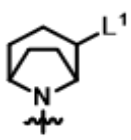
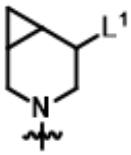
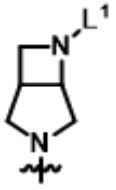
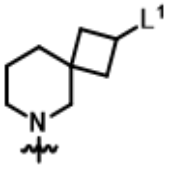
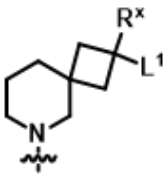
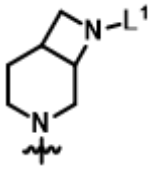
12. The compound or salt of claim 11, wherein B-L^1 is  ,  or  .

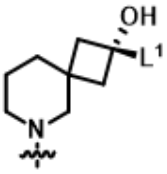
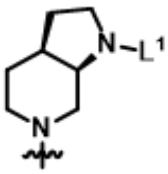
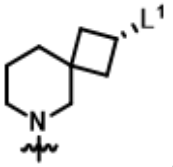
13. The compound or salt of any one of claims 2-9, wherein X is CH_2.

14. The compound or salt of claim 13, wherein n is 0 and m is 1; n is 1 and m is 0; n is 1 and m is 1; n is 1 and m is 2 or n is 2 and m is 1.

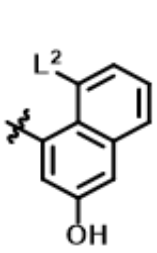
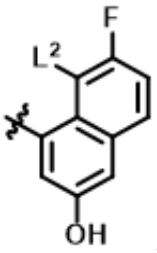
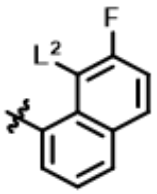
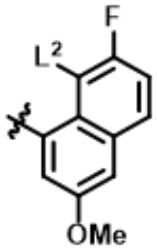
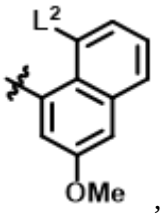
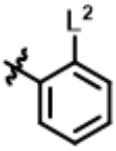
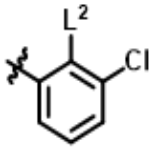
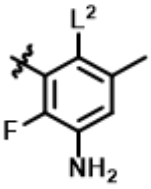
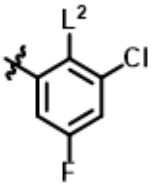
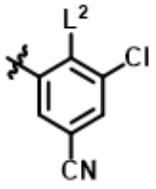
15. The compound or salt of claim 14, wherein  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  .

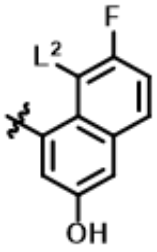
16. The compound or salt of claim 15, wherein B-L^1 is  ,  ,  ,  ,  or  .

17. The compound or salt of claim 1, wherein B-L^1 is , , , , , , , , , , ,  or .

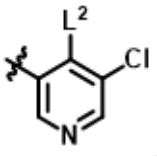
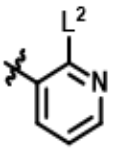
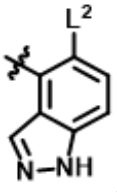
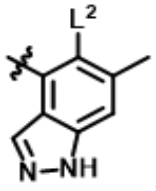
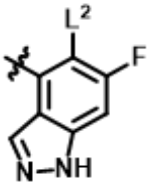
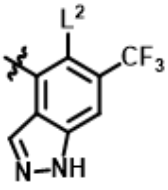
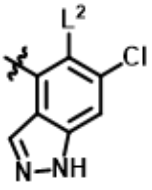
18. The compound or salt of claim 17, wherein B-L^1 is ,  or .

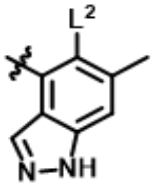
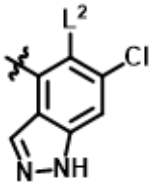
19. The compound or salt of any one of claims 1-17, wherein A is C_{6-10} aryl.

20. The compound or salt of claim 19, wherein A-L^2 is , , , , , , , , , , or .

21. The compound or salt of claim 20, wherein A-L^2 is .

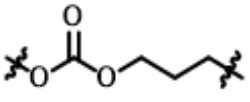
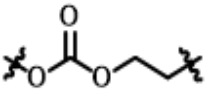
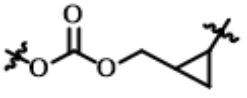
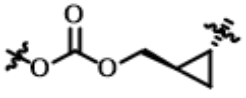
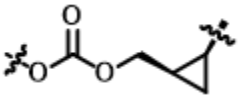
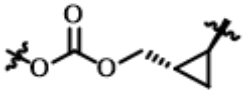
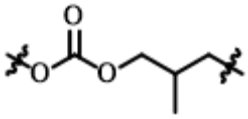
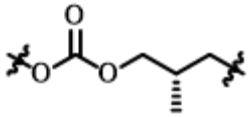
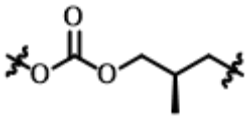
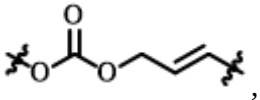
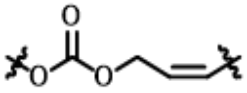
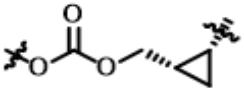
22. The compound or salt of any one of claims 1-18, wherein A-L^2 is 5-10 membered heteroaryl.

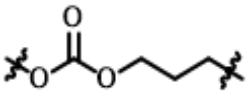
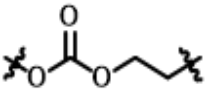
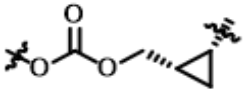
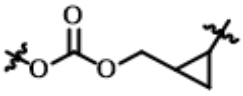
23. The compound or salt of claim 22, wherein A-L^2 is , , , , , , or .

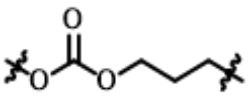
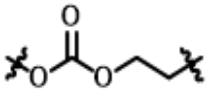
24. The compound or salt of claim 23, wherein A-L^2 is  or .

25. The compound or salt of any one of claims 1-24, wherein -L^1-L^2- is -O-C(O)-O-L^2.

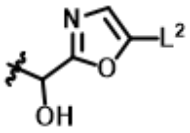
26. The compound or salt of claim 25, wherein L^2 is ethylene, n-propylene, 2-methyl-*n*-propylene, cis-2-propenylene, trans-2-propenylene or -CH_2-cyclopropylene.

27. The compound or salt of claim 26, wherein -L^1-L^2- is , , , , , , , , , ,  or .

28. The compound or salt of claim 27, wherein -L^1-L^2- is , ,  or .

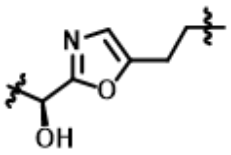
29. The compound or salt of claim 28, wherein -L^1-L^2- is  or .

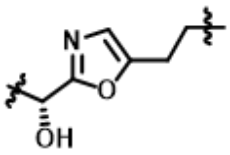
30. The compound or salt of any one of claims 1-24, wherein -L^1-L^2- is a -C_{1-4} hydroxyalkylene-5-6 membered heteroaryl-L^2.

31. The compound or salt of claim 30, wherein -L^1-L^2- is 

.

32. The compound or salt of claim 31, wherein L^2 is ethylene.

33. The compound or salt of claim 32, wherein -L^1-L^2- is 

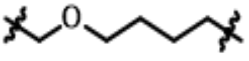
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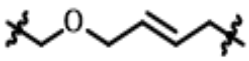
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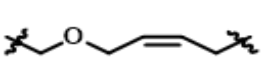
34. The compound or salt of any one of claims 1-24, wherein -L^1-L^2- is -C_{1-4} alkylene-O-L^2.

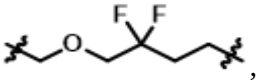
35. The compound or salt of claim 34, wherein -L^1-L^2- is -methylene-O-L^2.

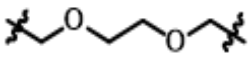
36. The compound or salt of claim 35, wherein L^2 is *n*-butylene, 2,2-difluoro-*n*-butylene, trans-2-butenylene, cis-2-butenylene, 3-methyl-*n*-butylene, -ethylene-cyclopropylene- or ethylene-O-methylene.

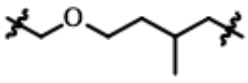
37. The compound or salt of claim 36, wherein -L^1-L^2- is 

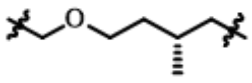
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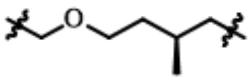
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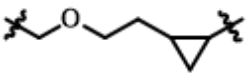
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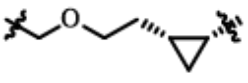
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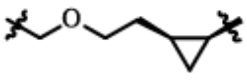
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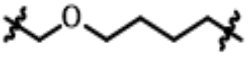
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or 

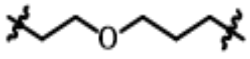
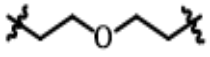
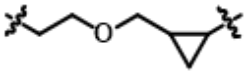
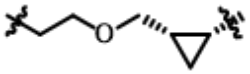
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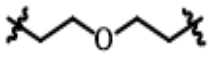
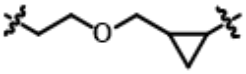
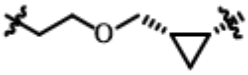
38. The compound or salt of claim 37, wherein -L^1-L^2- is 

.

39. The compound or salt of claim 34, wherein -L^1-L^2- is ethylene-O-L^2.

40. The compound or salt of claim 39, wherein L^2 is ethylene, *n*-propylene or methylene-cyclopropylene.

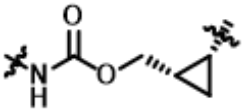
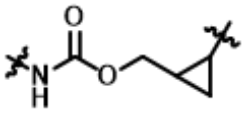
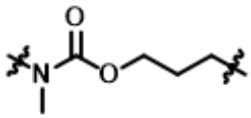
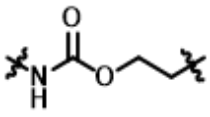
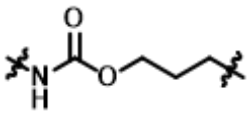
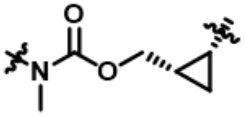
41. The compound or salt of claim 40, wherein -L^1-L^2- is , ,  or .

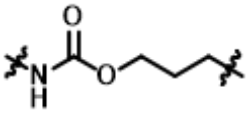
42. The compound or salt of claim 41, wherein -L^1-L^2- is ,  or .

43. The compound or salt of any one of claims 1-24, wherein -L^1-L^2- is -NR^z-C(O)-O-L^2.

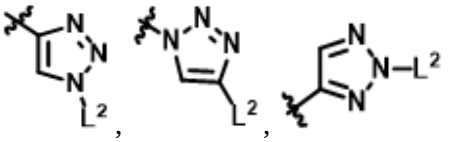
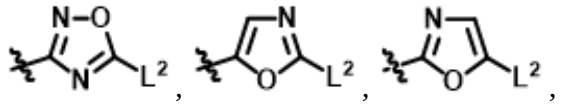
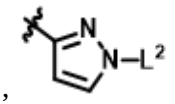
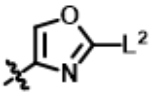
44. The compound or salt of claim 43, wherein R^z is hydrogen or methyl.

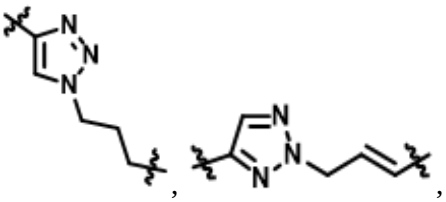
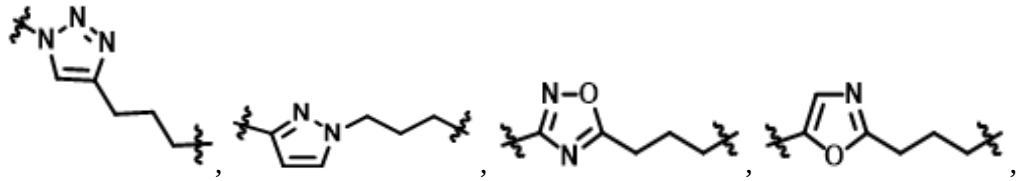
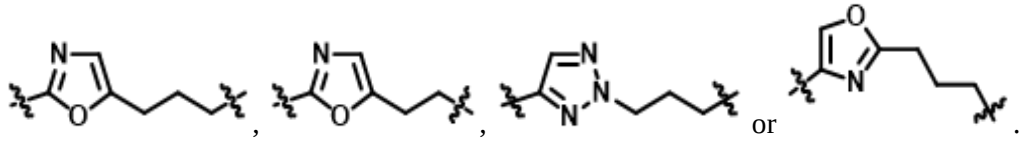
45. The compound or salt of claim 43 or 44, wherein L^2 is *n*-propylene, ethylene, -CH_2-cyclopropylene.

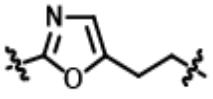
46. The compound or salt of claim 45, wherein -L^1-L^2- is , , , ,  or .

47. The compound or salt of claim 46, wherein -L^1-L^2- is .

48. The compound or salt of any one of claims 1-24, wherein -L^1-L^2- is a 5-6 membered heteroaryl.

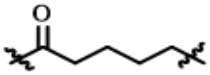
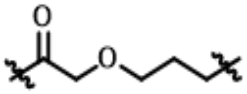
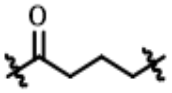
49. The compound or salt of claim 48, wherein -L^1-L^2- is , ,  or .

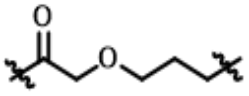
50. The compound or salt of claim 49, wherein -L^1-L^2- is , ,  or .

51. The compound or salt of claim 50, wherein -L^1-L^2- is .

52. The compound or salt of any one of claims 1-24, wherein -L^1-L^2- is -C(O)-.

53. The compound or salt of claim 52, wherein L^2 is *n*-propylene, -methylene-O-*n*-propylene or *n*-butylene.

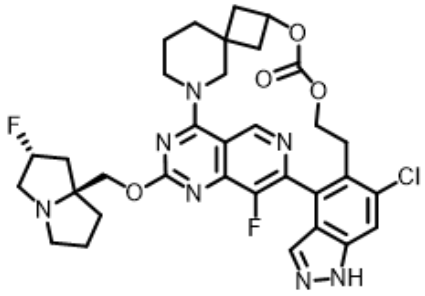
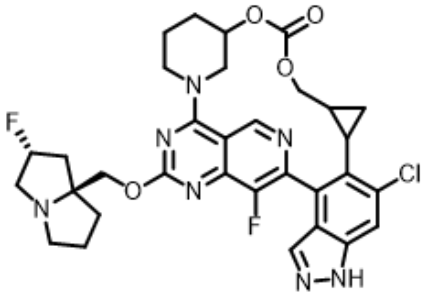
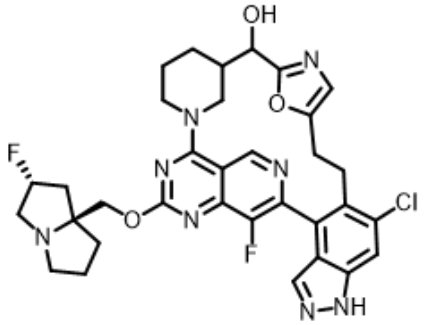
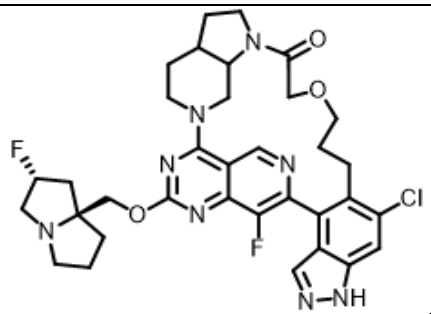
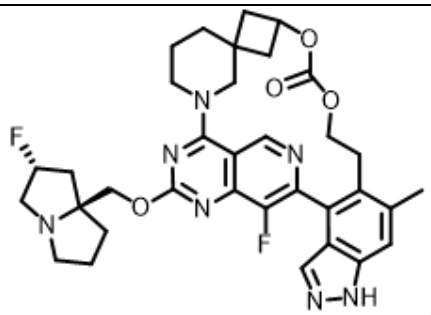
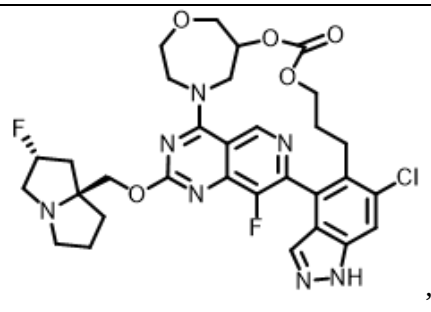
54. The compound or salt of claim 53, wherein -L^1-L^2- is ,  or .

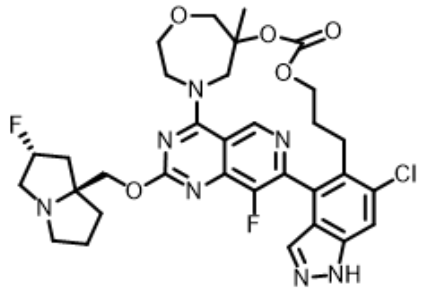
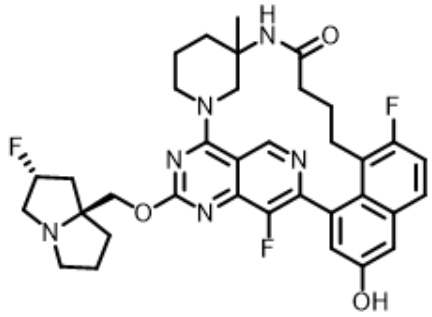
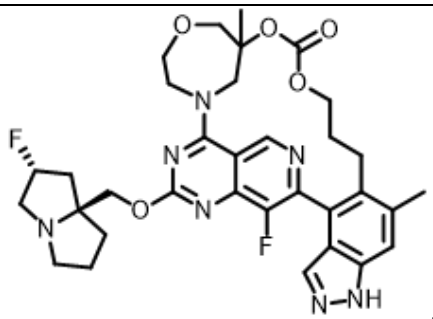
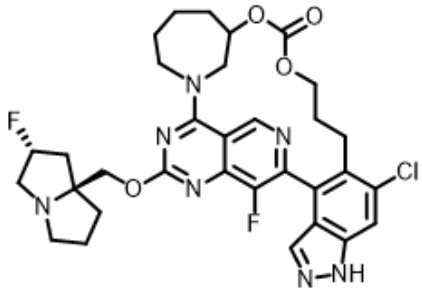
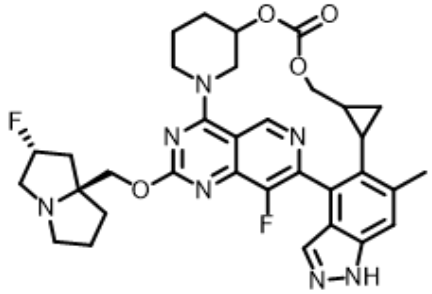
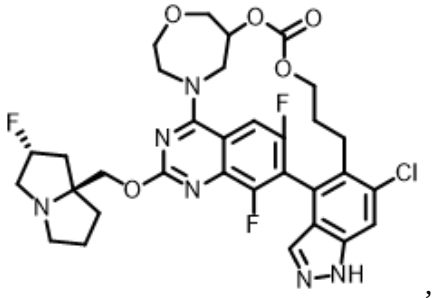
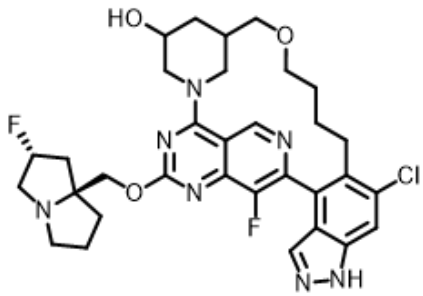
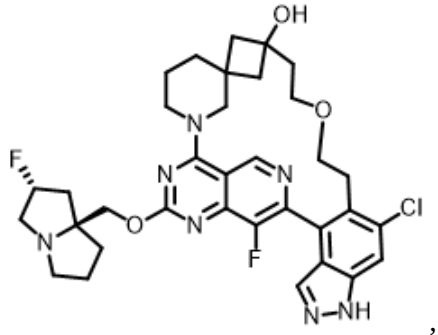
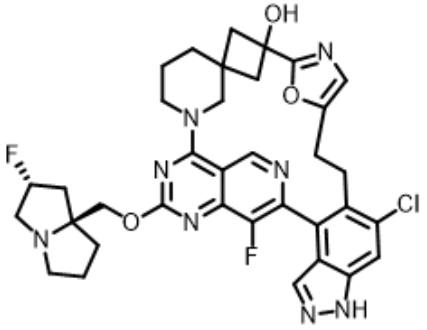
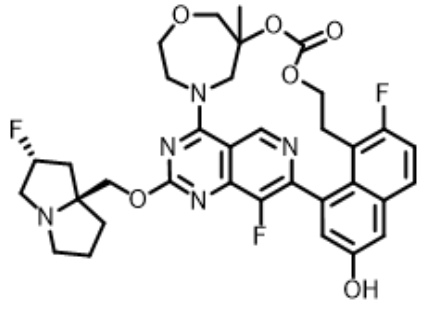
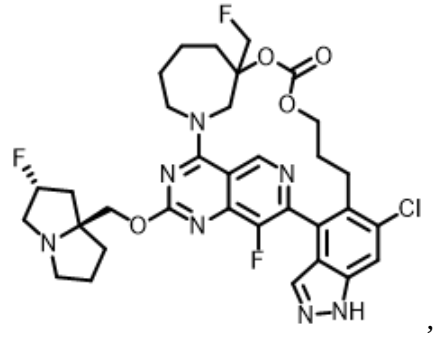
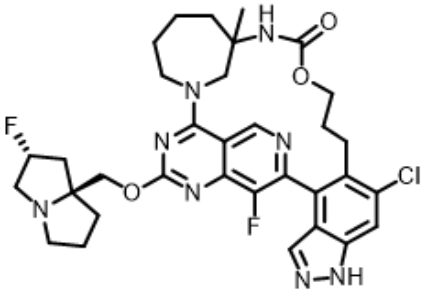
55. The compound or salt of claim 54, wherein -L^1-L^2- is .

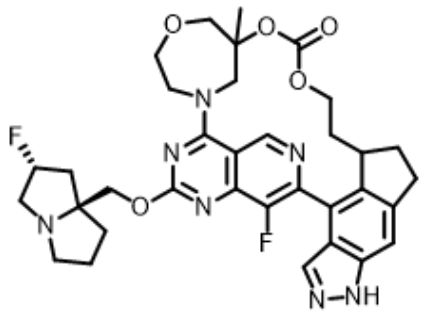
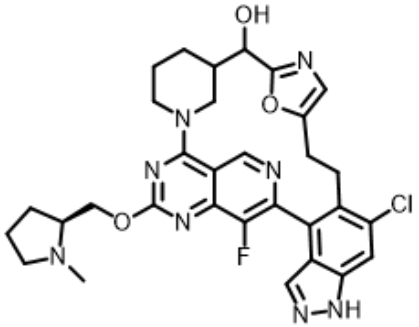
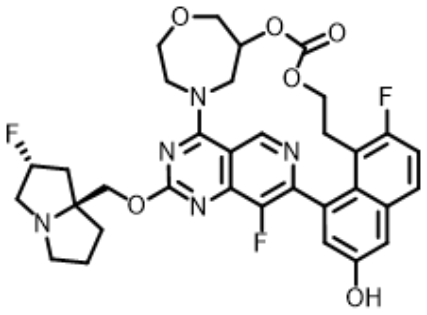
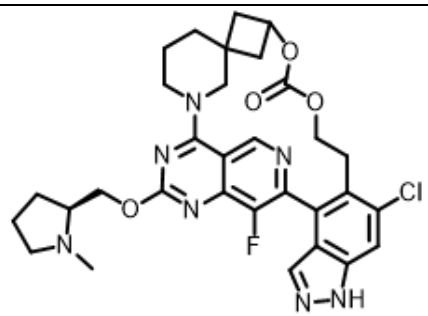
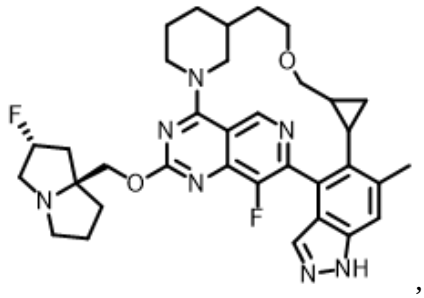
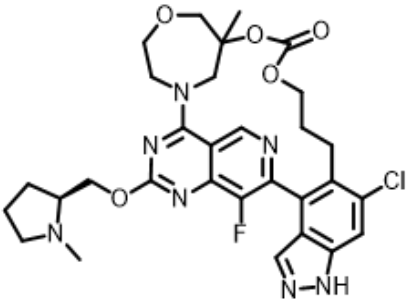
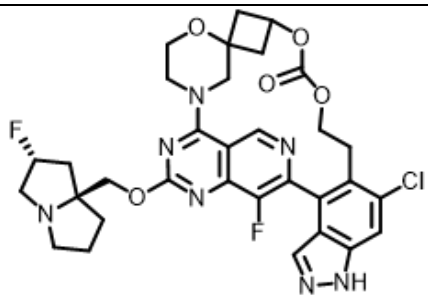
56. The compound or salt of any one of claims 1-55, wherein R^4 is C_{1-4} alkyl or halogen.

57. The compound or salt of claim 56, wherein R^4 is fluorine.

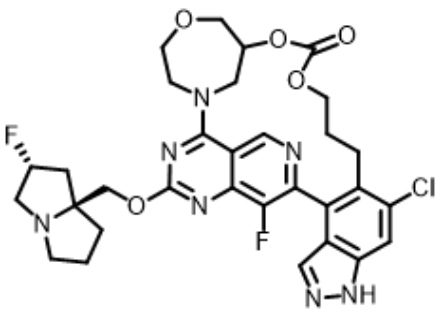
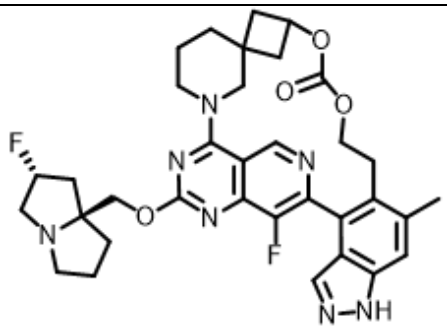
58. The compound or salt of claim 1 or 2, wherein the compound is:

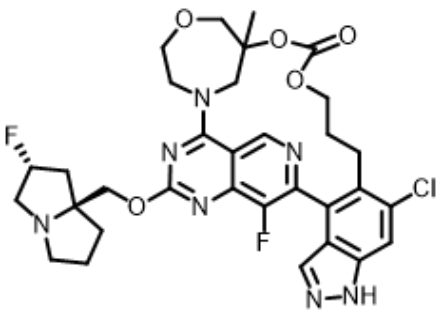
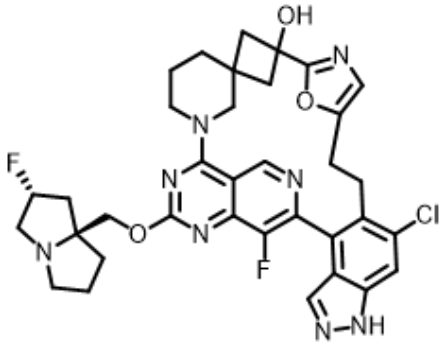
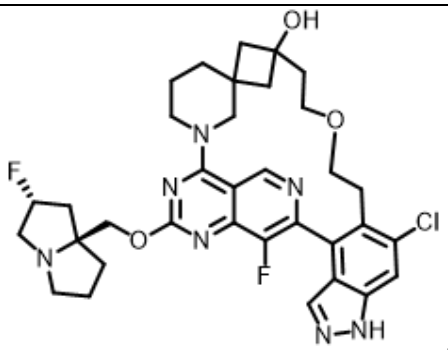
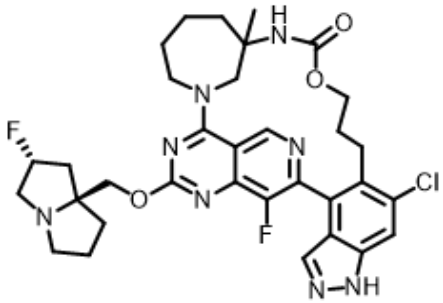
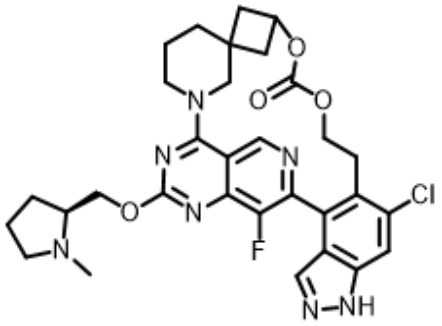
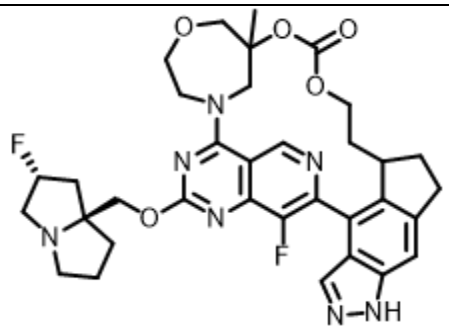
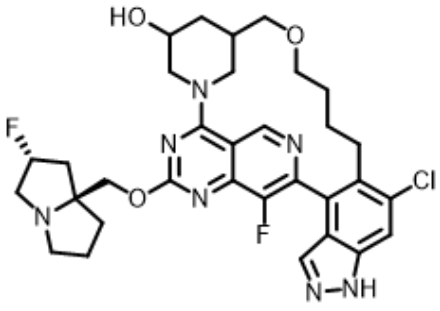
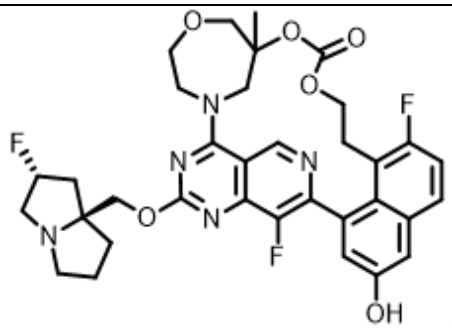
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Compound	Compound	Compound
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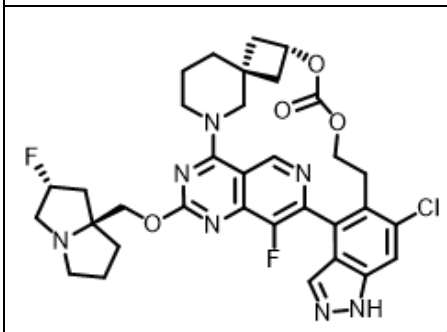
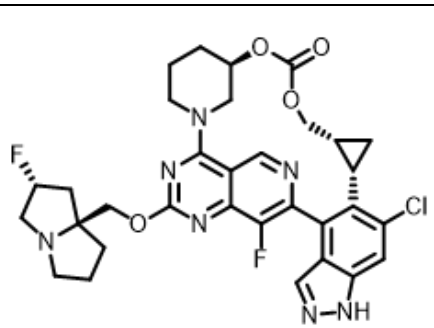
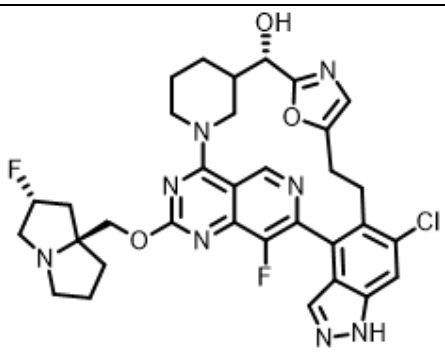
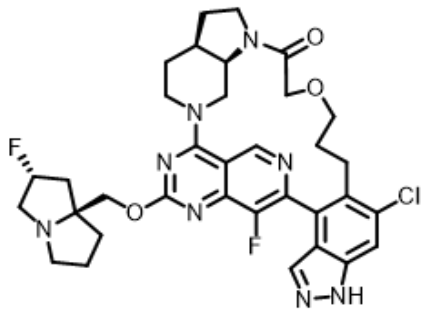
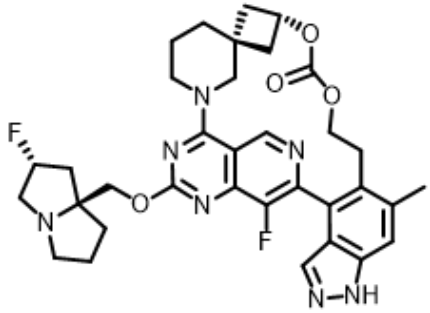
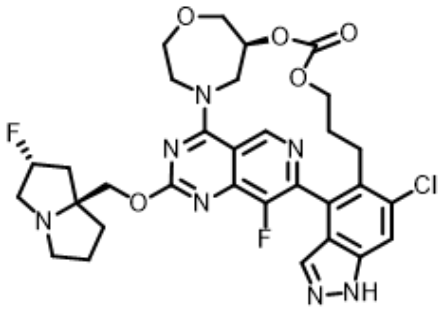
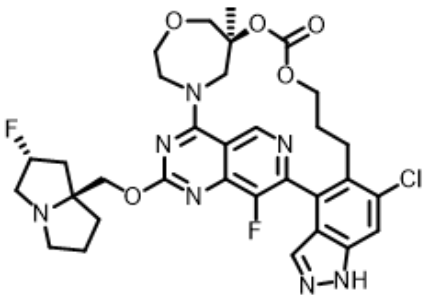
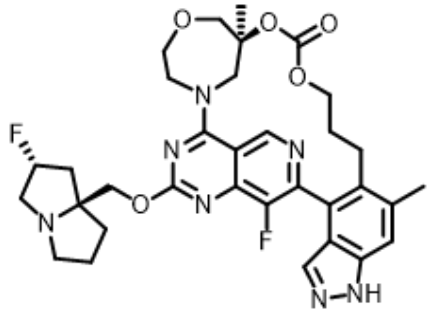
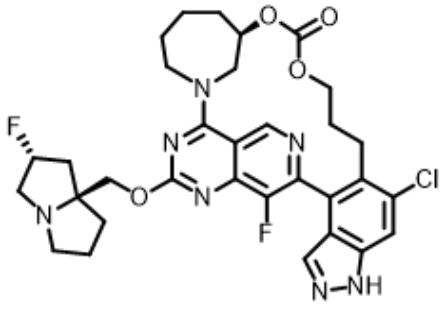
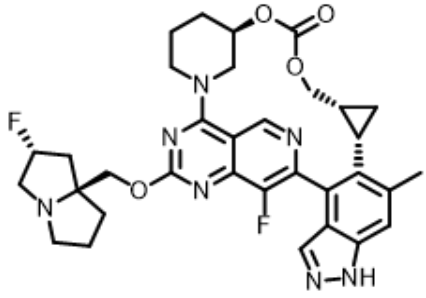
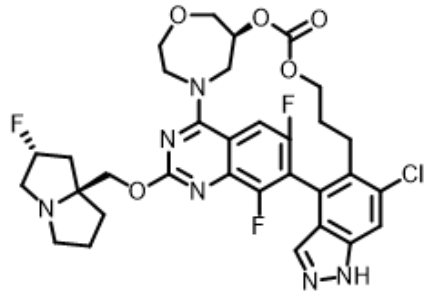
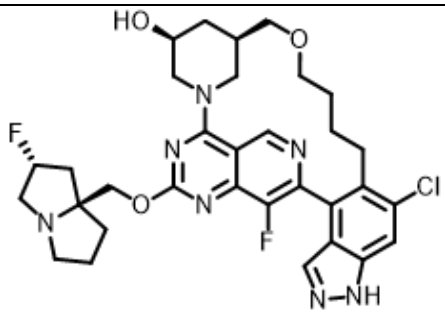
Compound	Compound	Compound
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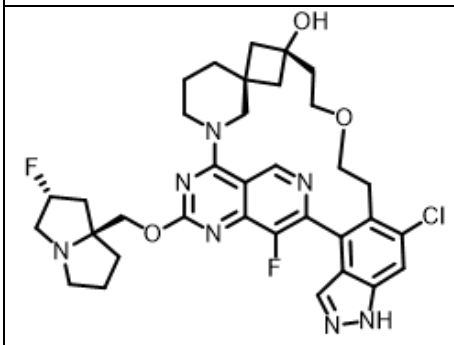
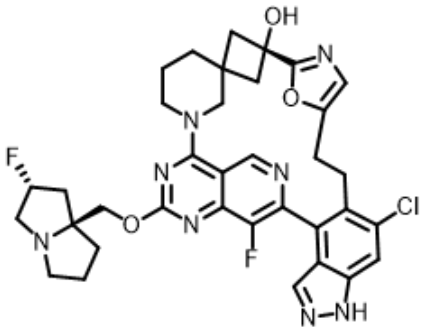
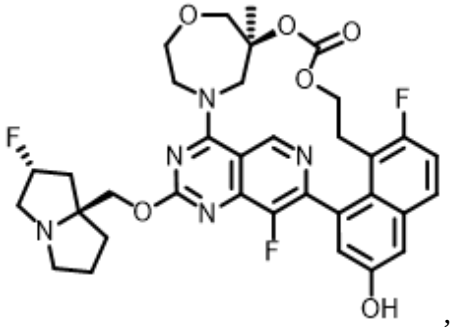
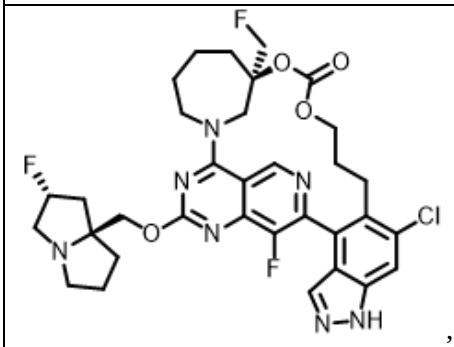
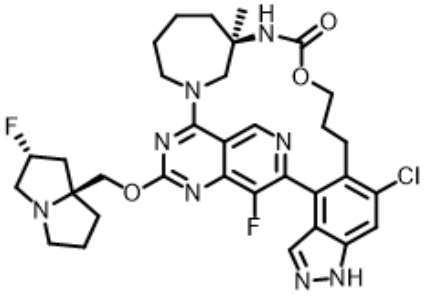
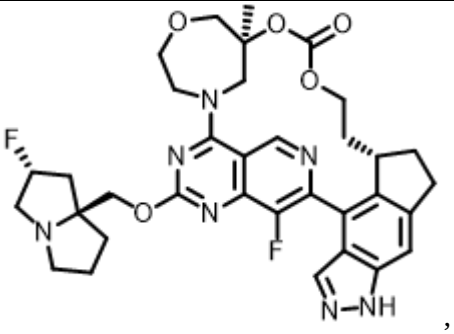
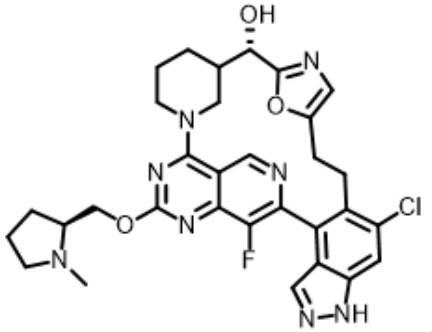
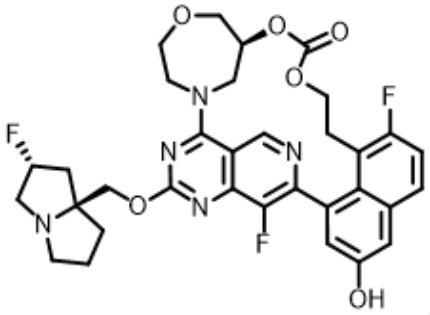
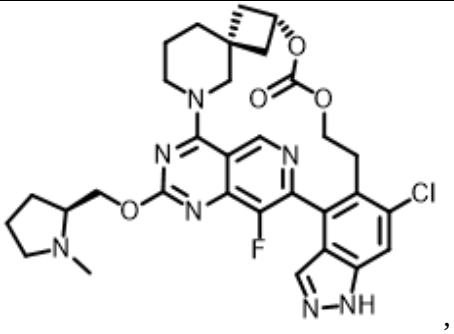
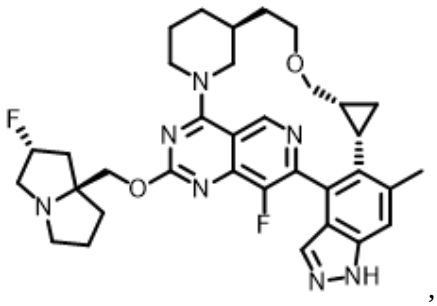
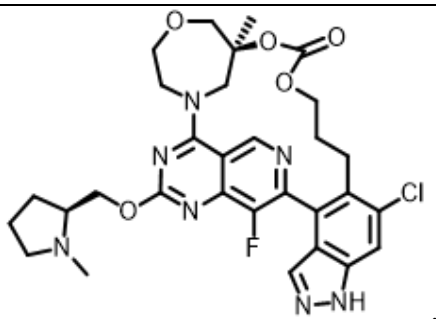
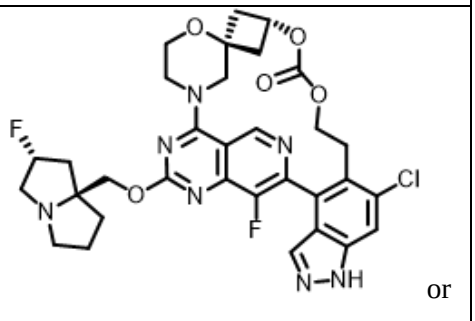
59. The compound or salt of claim 1 or 2, wherein the compound is:

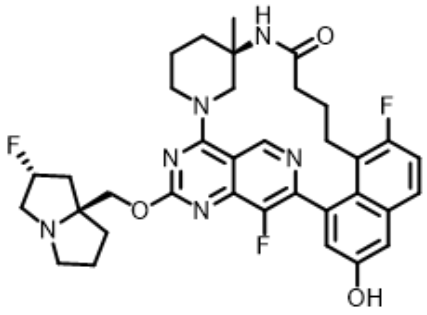
Compound	Compound
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Compound	Compound
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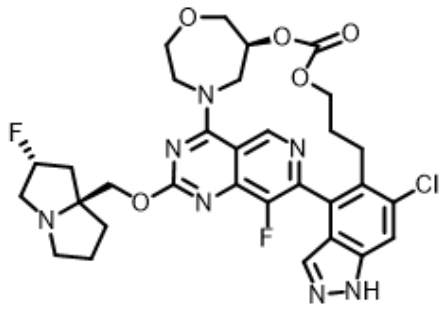
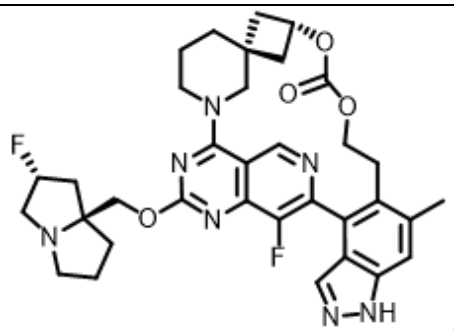
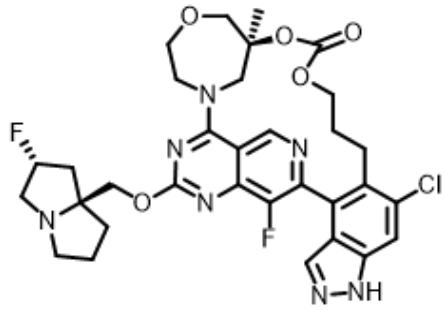
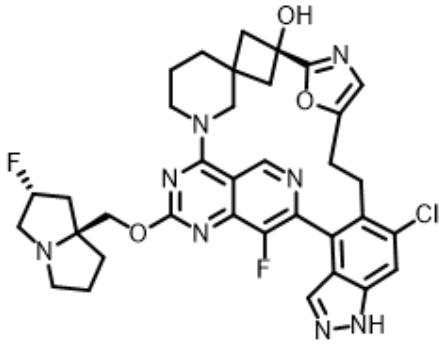
60. The compound or salt of claim 1 or 2, wherein the compound is:

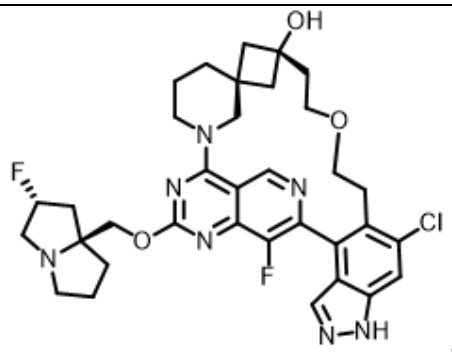
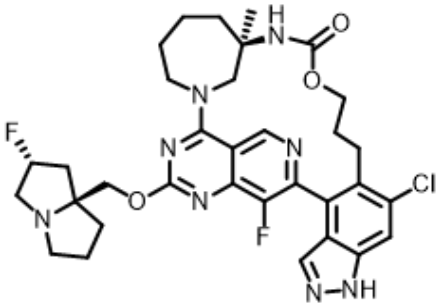
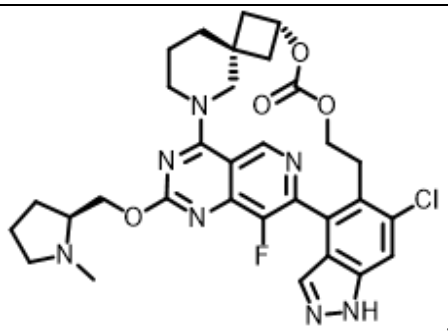
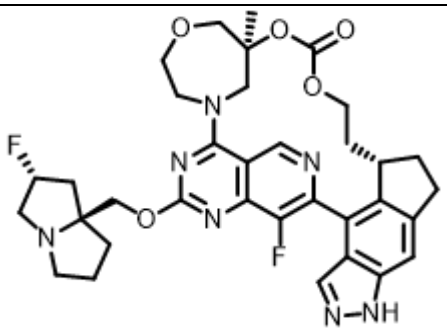
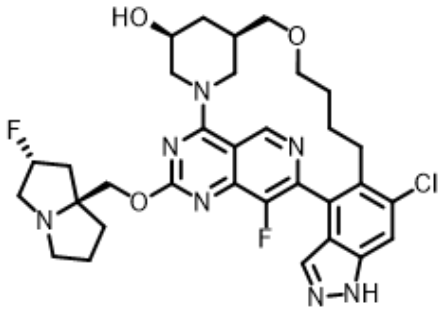
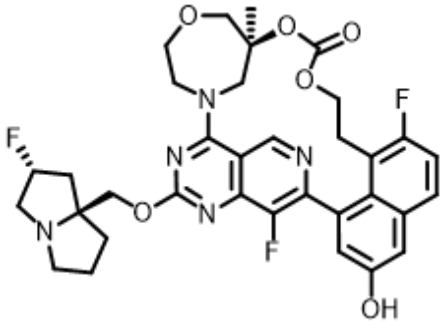
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Compound	Compound	Compound
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Compound	Compound	Compound
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61. The compound or salt of claim 1 or 2, wherein the compound is:

Compound	Compound
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Compound	Compound
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 or	 .

62. A pharmaceutical composition comprising the compound or salt according to any one of claims 1-61 and a pharmaceutically acceptable excipient.

63. A compound or salt according to any one of claims 1-61 or the pharmaceutical composition according to claim 62 for use as a medicament.

64. Use of the compound or salt according to any one of claims 1-61 or the pharmaceutical composition according to claim 62 in the preparation of a medicament for treating cancer.

65. Use of the compound or salt according to any one of claims 1-61 or the pharmaceutical composition according to claim 62 in the preparation of a medicament for treating cancer, wherein one or more cells of the cancer express a KRAS G12D mutant protein.

66. The use according to claim 64 or 65, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.