KRAS G12C INHIBITORS AND METHODS OF USING THE SAME

FIELD OF INVENTION

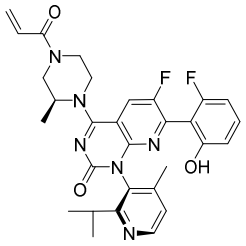
[0001] Provided herein are KRAS G12C inhibitors, composition of the same, and methods of using the same. These inhibitors are useful for treating a number of disorders, including pancreatic, colorectal, and lung cancers.

BACKGROUND

[0002] KRAS gene mutations are common in pancreatic cancer, lung adenocarcinoma, colorectal cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. KRAS mutations are also observed in about 25% of patients with NSCLC, and some studies have indicated that KRAS mutations are a negative prognostic factor in paptients with NSCLC. Recently, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations have been found to confer resistance to epidermal growth factor receptor (EGFR) targeted therapies in colorectal cancer; accordingly, the mutational status of KRAS can provide important information prior to the prescription of TKI therapy. Taken together, there is a need for new medical treatments for patients with pancreatic cancer, lung adenocarcinoma, or colorectal cancer, especially those who have been diagnosed to have such cancers characterized by a KRAS mutation, and including those who have progressed after chemotherapy.

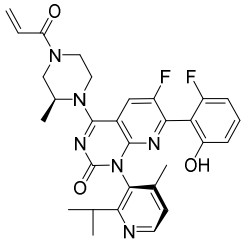
SUMMARY

[0002a] In one aspect, the present disclosure provides



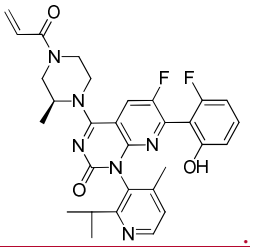
a compound, wherein the compound is or a pharmaceutically acceptable salt thereof.

[0002b] In one aspect, the present disclosure provides

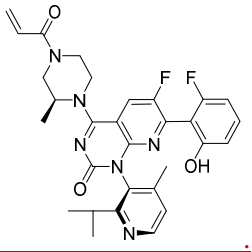


a compound, wherein the compound is or a pharmaceutically acceptable salt thereof.

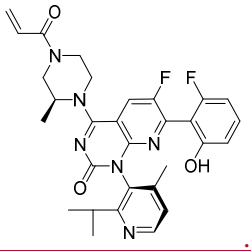
[0002c] In one aspect, the present disclosure provides

a compound wherein the compound is  .

[0002d] In one aspect, the present disclosure provides

a compound, wherein the compound is  .

[0002e] In one aspect, the present disclosure provides

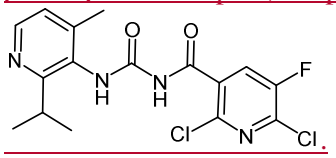
a compound, wherein the compound is  .

[0002f] In one aspect, the present disclosure provides a pharmaceutical composition comprising the compound according to the disclosure and a pharmaceutically acceptable excipient.

[0002g] In one aspect, the present disclosure provides an *in vitro* method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of the disclosure or the composition of the disclosure.

[0002h] In one aspect, the present disclosure provides a use of the compound of the disclosure in the manufacture of a medicament for treating cancer in a subject.

[0002i] In one aspect, the present disclosure provides a compound, wherein the compound is



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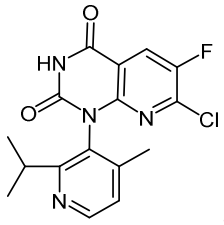
[0002j] In one aspect, the present disclosure provides a compound, wherein the compound is



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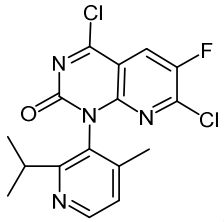
[0002k] In one aspect, the present disclosure provides a compound, wherein the compound is



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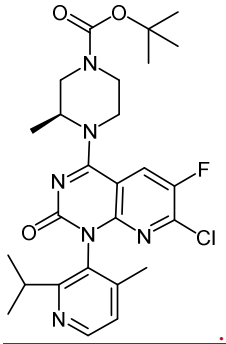
[0002l] In one aspect, the present disclosure provides a compound, wherein the compound is



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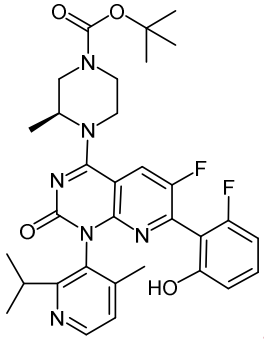
[0002m] In one aspect, the present disclosure provides a compound, wherein the compound is



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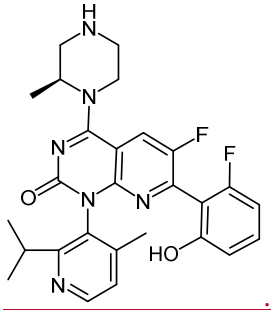
[0002n] In one aspect, the present disclosure provides a compound, wherein the compound is



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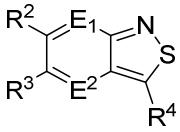
[0002o] In one aspect, the present disclosure provides a process for preparing a compound of the disclosure, comprising providing a compound according to the disclosure and converting it into a compound of the disclosure.

[0003] Provided herein are compound having a structure of formula (I)



(I)

wherein

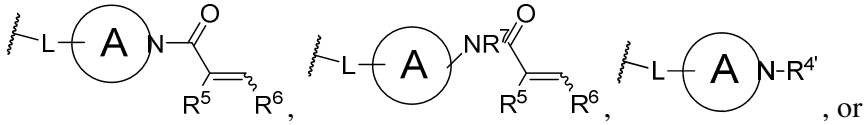
E^1 and E^2 are each independently N or CR^1;

R^1 is independently H, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, NH-C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, cyano, or halo;

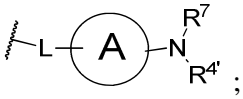
R^2 is halo, C_{1-6}alkyl, C_{1-6}haloalkyl, OR', N(R')$_2$, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-3} alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, aryl, heteroaryl, C_{0-3} alkylenearyl, or C_{0-3} alkyleneheteroaryl, and each R' is independently H, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, $C_{1–3}$alkyl, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–4}$cycloalkyl, $C_{2–3}$ alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl;

R^4 is



, or

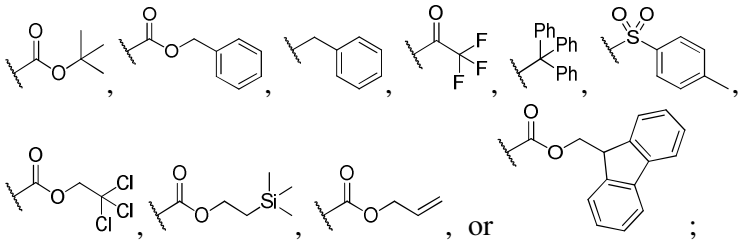


;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, C_{1-6}alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

$R^{4'}$ is H, $C_{1–6}$alkyl, C_{2-6}alkynyl, $C_{1–6}$alkylene-O-C_{1-4}alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$ haloalkyl, cycloalklyl, heterocycloalkyl, $C_{0–3}$alkylene-$C_{3–4}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$ heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-C_{6-14}aryl, or selected from



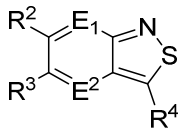
, or ;

R^5 and R^6 are each independently H, halo, $C_{1–6}$alkyl, C_{2-6}alkynyl, $C_{1–6}$ alkylene-O-C_{1-4}alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, $C_{0–6}$ alkylene-amide, $C_{0–3}$alkylene-C(O)OH, $C_{0–3}$alkylene-C(O)OC_{1-4}alkyl, $C_{1–6}$ alkylene-O-aryl, $C_{0–3}$alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring; and

R^7 is H or $C_{1–8}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring,

or a pharmaceutically acceptable salt thereof.

[0004] In another ~~embodiment~~example, provided herein are compounds having a structure of formula (I)



(I)

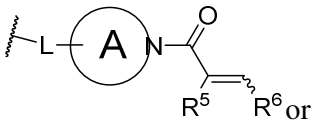
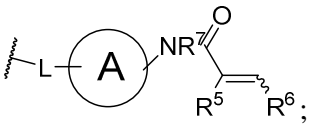
wherein

E^1 and E^2 are each independently N or CR^1;

R^1 is independently H, hydroxy, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, C_{1-6}alkoxy, NH-C_{1-6}alkyl, N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', N(R')$_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-C_{6-14}aryl, or $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, $C_{1–3}$alkyl, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–14}$cycloalkyl, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl;

R^4 is  or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

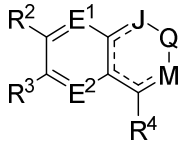
L is a bond, C_{1-6}alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^5 and R^6 are each independently H, halo, $C_{1–8}$alkyl, C_{2-8}alkynyl, $C_{1–6}$ alkylene-O-C_{1-4}alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, $C_{0–6}$ alkylene-amide, $C_{0–3}$alkylene-C(O)OH, $C_{0–3}$alkylene-C(O)OC_{1-4}alkyl, $C_{1–6}$ alkylene-O-aryl, $C_{0–3}$alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring; and

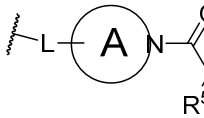
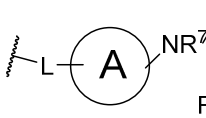
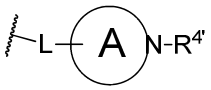
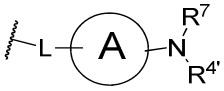
R^7 is H or $C_{1–6}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring,

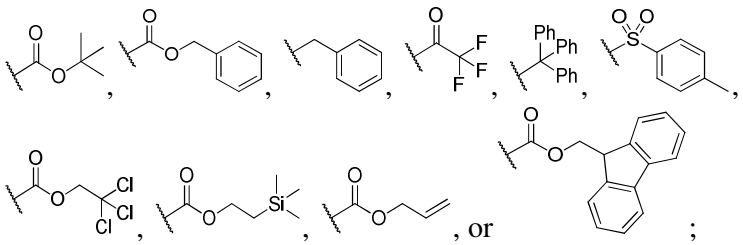
or a pharmaceutically acceptable salt thereof.

[0005] Further provided are compounds of formula (II), or a pharmaceutically acceptable salt thereof:



(II)

wherein E^1 and E^2 are each independently N or CR^1; J is N, NR^{10}, or CR^{10}; M is N, NR^{13}, or CR^{13}; ⎓ is a single or double bond as necessary to give every atom its normal valence; R^1 is independently H, hydroxy, $C_{1–6}$alkyl, $C_{1–4}$haloalkyl, C_{1-4}alkoxy, NH-C_{1-4}alkyl, N(C_{1-4}alkyl)$_2$, cyano, or halo; R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', N(R')$_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-C_{6-14}aryl, or $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring; R^3 is halo, $C_{1–3}$alkyl, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–4}$cycloalkyl, C_{2-14}heterocycloalkyl, $C_{2–3}$ alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl; R^4 is  ,  ,  , or  ; ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring; L is a bond, C_{1-6}alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH; $R^{4'}$ is H, $C_{1–8}$alkyl, C_{2-8}alkynyl, $C_{1–6}$alkylene-O-C_{1-4}alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$ haloalkyl, cycloalklyl, heterocycloalkyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$ heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-C_{6-14}aryl, or selected from



R^5 and R^6 are each independently H, halo, $C_{1–6}$alkyl, C_{2-6}alkynyl, $C_{1–6}$ alkylene-O-C_{1-4}alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, $C_{0–6}$ alkylene-amide, $C_{0–}$

$_3$alkylene-C(O)OH, $C_{0–3}$alkylene-C(O)OC_{1-4}alkyl, $C_{1–6}$ alkylene-O-aryl, $C_{0–3}$alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring; R^7 is H or $C_{1–8}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring; Q is CR^8R^9, $C=CR^8R^9$, C=O, C=S, or $C=NR^8$; R^8 and R^9 are each independently H, $C_{1–3}$alkyl, hydroxy, $C_{1–3}$alkoxy, cyano, nitro, or $C_{3–6}$cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring; R^{10} is $C_{1–8}$alkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{3–14}$heteroaryl, $C_{0–3}$ alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{1–6}$alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-$C_{3–14}$heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, NH-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-3}alkylene-C_{6-14}aryl, NH-C_{0-3}alkylene-$C_{2–14}$heteroaryl, NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or $C_{1–6}$alkylene-amine; and

R^{13} is $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, or $C_{3–14}$cycloalkyl,

or a pharmaceutically acceptable salt thereof, with the proviso that

(1) when J is NR^{10}, M is N or CR^{13};

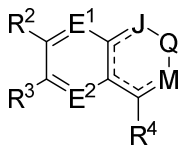
(2) when M is NR^{13}, J is N or CR^{10};

(3) when J is CR^{10}, M is N or NR^{13}; and

(4) when M is CR^{13}, J is N or NR^{10}.

[0006] In some ~~embodiment~~examples, when Q is C=O, and E^1 and E^2 are each CR^1; then either (1) R^{10} is $C_{1–3}$alkylenearyl, $C_{1–3}$alkyleneheteroaryl, $C_{0–3}$alkylene-$C_{3–8}$cycloalkyl, $C_{1–3}$alkylene-$C_{2–7}$heterocycloalkyl, or halo; or (2) R^{13} is $C_{1–3}$haloalkyl or $C_{3–5}$cycloalkyl. In various ~~embodiment~~examples, J is NR^{10} and M is CR^{13}. In some ~~embodiment~~examples, J is CR^{10} and M is NR^{13}. In some ~~embodiment~~examples, J is N and M is NR^{13}. In various ~~embodiment~~examples, J is NR^{10} and M is N.

[0007] Further provided are compounds having a structure of formula (II)



(II)

wherein

E^1 and E^2 are each independently N or CR^1;

J is N, NR^{10}, or CR^{10};

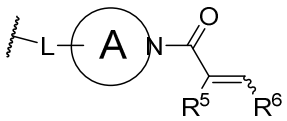
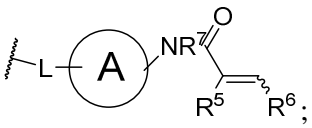
M is N, NR^{13}, or CR^{13};

--- is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, $C_{1–4}$alkyl, $C_{1–4}$haloalkyl, C_{1-4}alkoxy, NH-C_{1-4}alkyl, N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', N(R')$_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-C_{6-14}aryl, or $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, $C_{1–3}$alkyl, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–4}$cycloalkyl, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl;

R^4 is  or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, $C_{1–6}$alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^5 and R^6 are each independently H, halo, $C_{1–6}$alkyl, C_{2-6}alkynyl, $C_{1–6}$ alkylene-O-C_{1-4}alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, $C_{0–6}$ alkylene-amide, $C_{0–3}$alkylene-C(O)OH, $C_{0–3}$alkylene-C(O)OC_{1-4}alkyl, $C_{1–6}$ alkylene-O-aryl, $C_{0–3}$alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or $C_{1–8}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

Q is CR^8R^9, $C=CR^8R^9$, C=O, C=S, or $C=NR^8$;

R^8 and R^9 are each independently H, $C_{1–3}$alkyl, hydroxy, $C_{1–3}$alkoxy, cyano, nitro, or $C_{3–6}$cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

R^{10} is $C_{1–8}$alkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{3–14}$heteroaryl, $C_{0–3}$ alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{1–6}$alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-

C_{0-3}alkylene-C_{3-14}heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, NH-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-3}alkylene-C_{6-14}aryl, NH-C_{0-3}alkylene-C_{2-14}heteroaryl, NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or C_{1-6}alkylene-amine;

with the proviso that

(1) when J is NR^{10}, M is N or CR^{13};

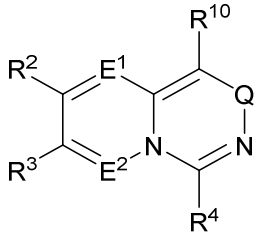
(2) when M is NR^{13}, J is N or CR^{10};

(3) when J is CR^{10}, M is N or NR^{13}; and

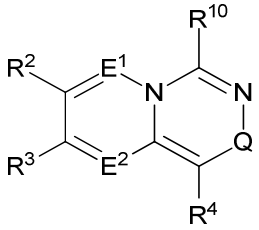
(4) when M is CR^{13}, J is N or NR^{10}.

[0008] In some ~~embodiment~~examples, when Q is C=O, and E^1 and E^2 are each CR^1; then either (1) R^{10} is C_{1-3}alkylenearyl, C_{1-3}alkyleneheteroaryl, C_{0-3}alkylene-C_{3-8}cycloalkyl, C_{1-3}alkylene-C_{2-7}heterocycloalkyl, or halo; or (2) R^{13} is C_{1-3}haloalkyl or C_{3-5}cycloalkyl. In various ~~embodiment~~examples, J is NR^{10} and M is CR^{13}. In some ~~embodiment~~examples, J is CR^{10} and M is NR^{13}. In some ~~embodiment~~examples, J is N and M is NR^{13}. In various ~~embodiment~~examples, J is NR^{10} and M is N.

[0009] Further provided are compounds of formula (III) or (III'), or a pharmaceutically acceptable salt thereof:



(III) or



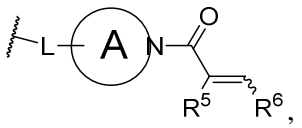
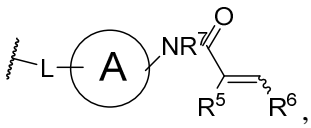
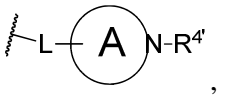
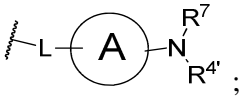
(III'),

wherein E^1 and E^2 are each independently N or CR^1;

R^1 is independently H, hydroxy, C_{1-6}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, NH-C_{1-4}alkyl, N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is halo, C_{1-6}alkyl, C_{1-6}haloalkyl, OR', N(R')$_2$, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or C_{0-3}alkylene-C_{2-14}heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

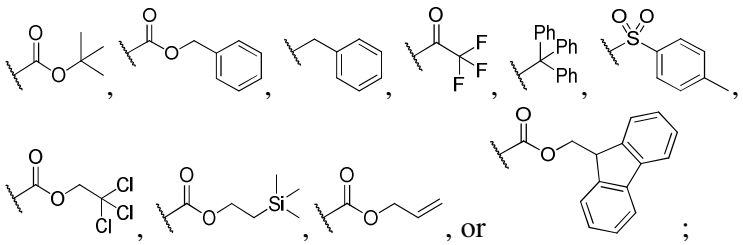
R^3 is halo, C_{1-3}alkyl, C_{1-2}haloalkyl, C_{1-3}alkoxy, C_{3-4}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3} alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl;

R^4 is  ,  ,  , or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, $C_{1\text{-}6}$alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for $C_{2\text{-}6}$alkylene, -O-$C_{2\text{-}5}$alkylene, -S-$C_{2\text{-}5}$alkylene, and NH-$C_{2\text{-}5}$ alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

$R^{4'}$ is H, $C_{1–8}$alkyl, $C_{2\text{-}8}$alkynyl, $C_{1–6}$alkylene-O-$C_{1\text{-}4}$alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$ haloalkyl, cycloalklyl, heterocycloalkyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$ heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, or selected from

 , or ;

R^5 and R^6 are each independently H, halo, $C_{1–6}$alkyl, $C_{2\text{-}6}$alkynyl, $C_{1–6}$ alkylene-O-$C_{1\text{-}4}$alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, $C_{0–6}$ alkylene-amide, $C_{0–3}$alkylene-C(O)OH, $C_{0–3}$alkylene-C(O)O$C_{1\text{-}4}$alkyl, $C_{1–6}$ alkylene-O-aryl, $C_{0–3}$alkylene-C(O)$C_{1\text{-}4}$alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or $C_{1–8}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

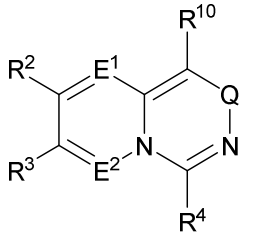
Q is CR^8R^9, $C{=}CR^8R^9$, C=O, C=S, or $C{=}NR^8$;

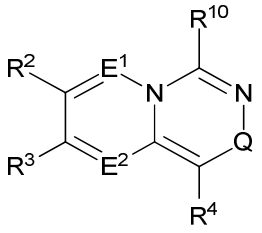
R^8 and R^9 are each independently H, $C_{1–6}$alkyl, hydroxy, $C_{1–6}$alkoxy, cyano, nitro, or $C_{3–14}$cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

R^{10} is $C_{1–8}$alkyl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, $C_{0–3}$alkylene-$C_{3–14}$heteroaryl, $C_{0–3}$ alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{1–6}$alkoxy, O-$C_{0\text{-}3}$ alkylene-$C_{6\text{-}14}$aryl,

O-C_{0-3}alkylene-$C_{3–14}$heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, NH-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-3}alkylene-C_{6-14}aryl, NH-C_{0-3}alkylene-$C_{2–14}$heteroaryl, NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or $C_{1–6}$alkylene-amine.

[0010] Further provided are compounds of formula (III) or (III'), or a pharmaceutically acceptable salt thereof:



(III) or


(III')

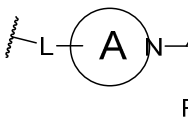
wherein

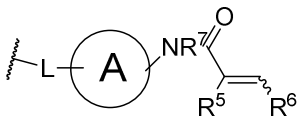
E^1 and E^2 are each independently N or CR^1;

R^1 is independently H, hydroxy, $C_{1–6}$alkyl, $C_{1–4}$haloalkyl, C_{1-4}alkoxy, NH-C_{1-4}alkyl, N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', N(R')$_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-C_{6-14}aryl, or $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, $C_{1–3}$alkyl, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–4}$cycloalkyl, C_{2-14}heterocycloalkyl, $C_{2–3}$ alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl;

R^4 is 

, **or** 

;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, C_{1-6}alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^5 and R^6 are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6} alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{1-6}alkyleneamine, C_{0-6} alkylene-amide, C_{0-3}alkylene-C(O)OH, C_{0-3}alkylene-C(O)OC_{1-4}alkyl, C_{1-6} alkylene-O-aryl, C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{2-14}heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or C_{1-8}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

Q is CR^8R^9, $C{=}CR^8R^9$, C=O, C=S, or $C{=}NR^8$;

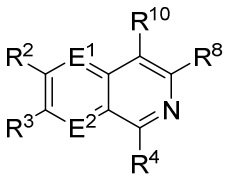
R^8 and R^9 are each independently H, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, cyano, nitro, or C_{3-14}cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

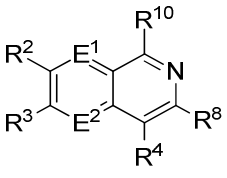
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{3-14}heteroaryl, C_{0-3} alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-C_{3-14}heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, NH-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-3}alkylene-C_{6-14}aryl, NH-C_{0-3}alkylene-C_{2-14}heteroaryl, NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or C_{1-6}alkylene-amine.

[0011] In some ~~embodiment~~examples, the compouds have a structure of formula (III). In other ~~embodiment~~examples, the compouds have a structure of formula (III').

[0012] The compounds of formula (II) or (III) as disclosed herein can have one or more of the following features. In some ~~embodiment~~examples, Q is C=O. In some ~~embodiment~~examples, Q is C=S. In some ~~embodiment~~examples, Q is $C{=}NR^8$. In various ~~embodiment~~examples, R^8 is C_{1-2}alkyl. In some ~~embodiment~~examples, Q is CR^8R^9. In various ~~embodiment~~examples, Q is $C{=}CR^8R^9$. In some ~~embodiment~~examples, R^8 and R^9, taken together with the carbon atom to which they are attached, form a 3–4 membered ring. In some ~~embodiment~~examples, R^8 is C_{1-2}alkyl, and R^9 is H.

[0013] Also provided are compounds of formula (IV) or (IV'), or a pharmaceutically acceptable salt thereof:



(IV) or


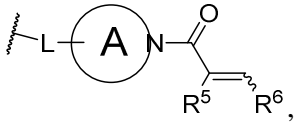
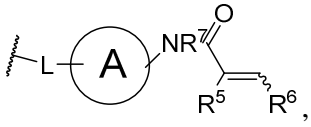
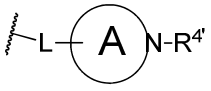
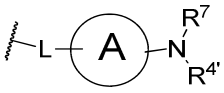
(IV') E^1 and E^2 are each independently CR^1 or N;

R^1 is independently H, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, NH-C_{1-6}alkyl,

$N(C_{1\text{-}6}alkyl)_2$, cyano, or halo;

R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', $N(R')_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, or $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R' is independently H, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}14}$cycloalkyl, $C_{2\text{-}14}$heterocycloalkyl, $C_{2\text{-}3}$alkenyl, $C_{2\text{-}3}$alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

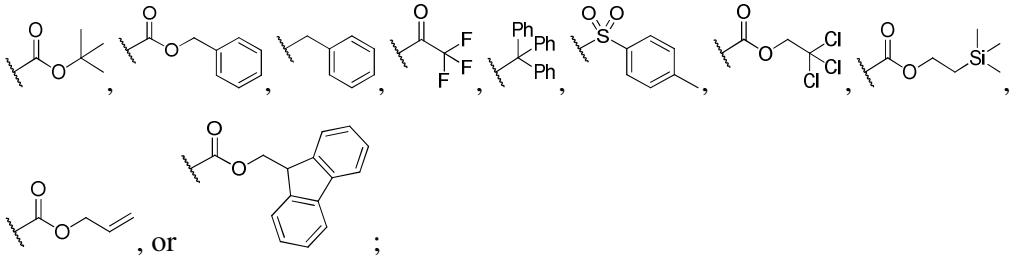
R^3 is halo, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–4}$cycloalkyl, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl;

R^4 is  ,  ,  , or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, $C_{1\text{-}6}$alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for $C_{2\text{-}6}$alkylene, -O-$C_{2\text{-}5}$alkylene, -S-$C_{2\text{-}5}$alkylene, and NH-$C_{2\text{-}5}$alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

$R^{4'}$ is H, $C_{1–8}$alkyl, $C_{2\text{-}8}$alkynyl, $C_{1–6}$alkylene-O-$C_{1\text{-}4}$alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$ haloalkyl, cycloalklyl, heterocycloalkyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$ heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, or selected from

 , or ;

R^5 and R^6 are each independently H, halo, $C_{1–6}$alkyl, $C_{2\text{-}6}$alkynyl, $C_{1–6}$ alkylene-O-$C_{1\text{-}4}$alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, $C_{0–6}$ alkylene-amide, $C_{0–3}$alkylene-C(O)OH, $C_{0–3}$alkylene-C(O)O$C_{1\text{-}4}$alkyl, $C_{1–6}$ alkylene-O-aryl, $C_{0–3}$alkylene-C(O)$C_{1\text{-}4}$alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6

membered ring;

R^7 is H or $C_{1–8}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

R^8 is H, $C_{1–3}$alkyl, hydroxy, $C_{1–3}$alkoxy, halo, cyano, nitro, $C_{3–14}$ cycloalkyl, or $NR^{11}R^{12}$;

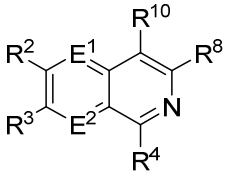
R^{11} and R^{12} are each independently H, $C_{1–8}$alkyl, or $C_{3–14}$cycloalkyl; and

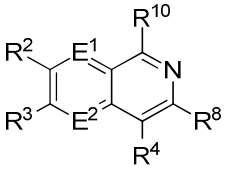
R^{10} is $C_{1\text{-}8}$alkyl, $C_{0\text{-}3}$alkylene-$C_{6\text{-}14}$aryl, $C_{0\text{-}3}$alkylene-$C_{2–14}$heteroaryl, $C_{0\text{-}3}$alkylene-$C_{3\text{-}14}$cycloalkyl, $C_{0\text{-}3}$alkylene-$C_{2\text{-}14}$heterocycloalkyl, $C_{1–6}$alkoxy, O-$C_{0\text{-}3}$alkylene-$C_{6\text{-}14}$aryl, O-$C_{0\text{-}3}$alkylene-$C_{2–14}$heteroaryl, O-$C_{0\text{-}3}$alkylene-$C_{3\text{-}14}$ cycloalkyl, O-$C_{0\text{-}3}$alkylene-$C_{2\text{-}14}$heterocycloalkyl, NH-$C_{1\text{-}8}$alkyl, N($C_{1\text{-}8}$alkyl)$_2$, NH-$C_{0\text{-}3}$alkylene-$C_{6\text{-}14}$aryl, NH-$C_{0\text{-}3}$alkylene-$C_{2–14}$heteroaryl, N-$C_{0\text{-}3}$alkylene-$C_{3\text{-}14}$ cycloalkyl, N-$C_{0\text{-}3}$alkylene-$C_{2\text{-}14}$heterocycloalkyl, halo, cyano, or $C_{1\text{-}6}$ alkylene-amine;

[0014] In some ~~embodiment~~examples, the compouds disclosed herein have a structure of formula (IV). In various ~~embodiment~~examples, the compouds disclosed herein have a structure of formula (IV'). In some ~~embodiment~~examples, E^1 and E^2 are each CR^1, and R^8 is hydroxy, halo, nitro, or $C_{3–6}$cycloalkyl.

[0015] In some ~~embodiment~~examples, R^8 is methyl.

Further provided are compounds having a structure of formula (IV) or (IV'):



(IV) or


(IV')

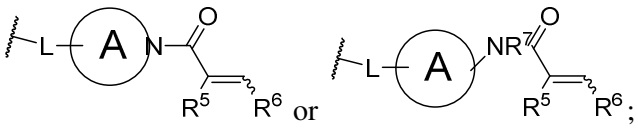
wherein

E^1 and E^2 are each independently CR^1 or N;

R^1 is independently H, hydroxy, $C_{1\text{-}6}$alkyl, $C_{1–6}$haloalkyl, $C_{1\text{-}6}$alkoxy, NH-$C_{1\text{-}6}$alkyl, N($C_{1\text{-}6}$alkyl)$_2$, cyano, or halo;

R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', N(R')$_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, or $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R' is independently H, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}14}$cycloalkyl, $C_{2\text{-}14}$heterocycloalkyl, $C_{2\text{-}3}$alkenyl, $C_{2\text{-}3}$alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–14}$cycloalkyl, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl;

R^4 is  or ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, C_{1-6}alkylene, -O-C_{0-5}alkylene, -S-C_{0-5}alkylene, or -NH-C_{0-5} alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^5 and R^6 are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6} alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{1-6}alkyleneamine, C_{0-6} alkylene-amide, C_{0-3}alkylene-C(O)OH, C_{0-3}alkylene-C(O)OC_{1-4}alkyl, C_{1-6} alkylene-O-aryl, C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{2-14}heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or C_{1-8}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

R^8 is H, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy, halo, cyano, nitro, C_{3-14} cycloalkyl, or $NR^{11}R^{12}$;

R^{11} and R^{12} are each independently H, C_{1-8}alkyl, or C_{3-15}cycloalkyl; and

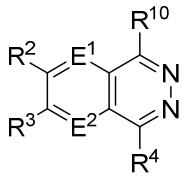
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{3-14}heteroaryl, C_{0-3} alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-C_{3-14}heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, NH-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-3}alkylene-C_{6-14}aryl, NH-C_{0-3}alkylene-C_{2-14}heteroaryl, NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or C_{1-6}alkylene-amine;

or a pharmaceutically acceptable salt thereof.

[0016] In some ~~embodiments~~example, the compouds disclosed herein have a structure of formula (IV). In various ~~embodiments~~example, the compouds disclosed herein have a structure of formula (IV'). In some ~~embodiments~~example, E^1 and E^2 are each CR^1, and R^8 is hydroxy, halo, nitro, or C_{3-6}cycloalkyl.

[0017] In some ~~embodiments~~example, R^8 is methyl.

[0018] Further provided are compounds having a structure of formula (V), or a pharmaceutically acceptable salt thereof:



(V)

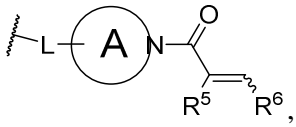
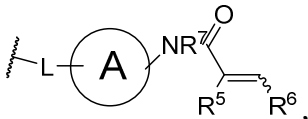
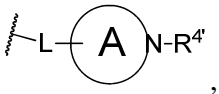
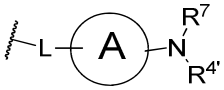
wherein

E^1 and E^2 are each independently CR^1 or N;

R^1 is independently H, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, NH-C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, cyano, or halo;

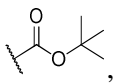
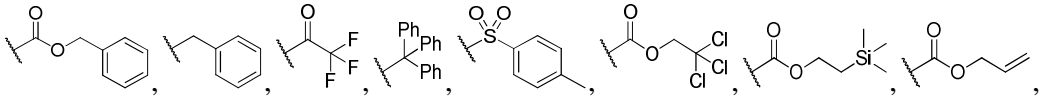
R^2 is halo, C_{1-6}alkyl, C_{1-6}haloalkyl, OR', N(R')$_2$, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or C_{0-3}alkylene-C_{2-14}heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

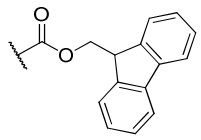
R^3 is halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-14}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, or heteroaryl;

R^4 is  ,  ,  , or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, C_{1-6}alkylene, -O-C_{0-5}alkylene, -S-C_{0-5}alkylene, or -NH-C_{0-5} alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

$R^{4'}$ is H, C_{1-8}alkyl, C_{2-8}alkynyl, C_{1-6}alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6} haloalkyl, cycloalklyl, heterocycloalkyl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or selected from  ,  , or

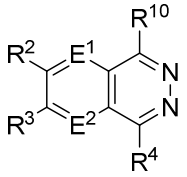

;

R^5 and R^6 are each independently H, halo, $C_{1–6}$alkyl, C_{2-6}alkynyl, $C_{1–6}$ alkylene-O-C_{1-4}alkyl, $C_{1–6}$alkylene-OH, $C_{1–6}$haloalkyl, $C_{1–6}$alkyleneamine, $C_{0–6}$ alkylene-amide, $C_{0–3}$alkylene-C(O)OH, $C_{0–3}$alkylene-C(O)OC_{1-4}alkyl, $C_{1–6}$ alkylene-O-aryl, $C_{0–3}$alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or $C_{1–8}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring; and

R^{10} is $C_{1–8}$alkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{3–14}$heteroaryl, $C_{0–3}$ alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{1–6}$alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-$C_{3–14}$heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, NH-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-3}alkylene-C_{6-14}aryl, NH-C_{0-3}alkylene-$C_{2–14}$heteroaryl, NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or $C_{1–6}$alkylene-amine; or a pharmaceutically acceptable salt thereof.

[0019] Further provided are compounds having a structure of formula (V):


(V)

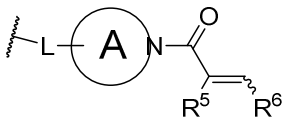
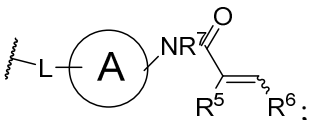
wherein

E^1 and E^2 are each independently CR^1 or N;

R^1 is independently H, hydroxy, C_{1-6}alkyl, $C_{1–6}$haloalkyl, C_{1-6}alkoxy, NH-C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, cyano, or halo;

R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', N(R')$_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$alkylene-C_{6-14}aryl, or $C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, $C_{1–6}$alkoxy, $C_{3–14}$cycloalkyl, $C_{2–8}$alkenyl, $C_{2–8}$alkynyl, aryl, or heteroaryl;

R^4 is  or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, C_{1-6}alkylene, -O-C_{0-5}alkylene, -S-C_{0-5}alkylene, or -NH-C_{0-5}alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5}alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^5 and R^6 are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6} alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{1-6}alkyleneamine, C_{0-6} alkylene-amide, C_{0-3}alkylene-C(O)OH, C_{0-3}alkylene-C(O)OC_{1-4}alkyl, C_{1-6} alkylene-O-aryl, C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{2-14}heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

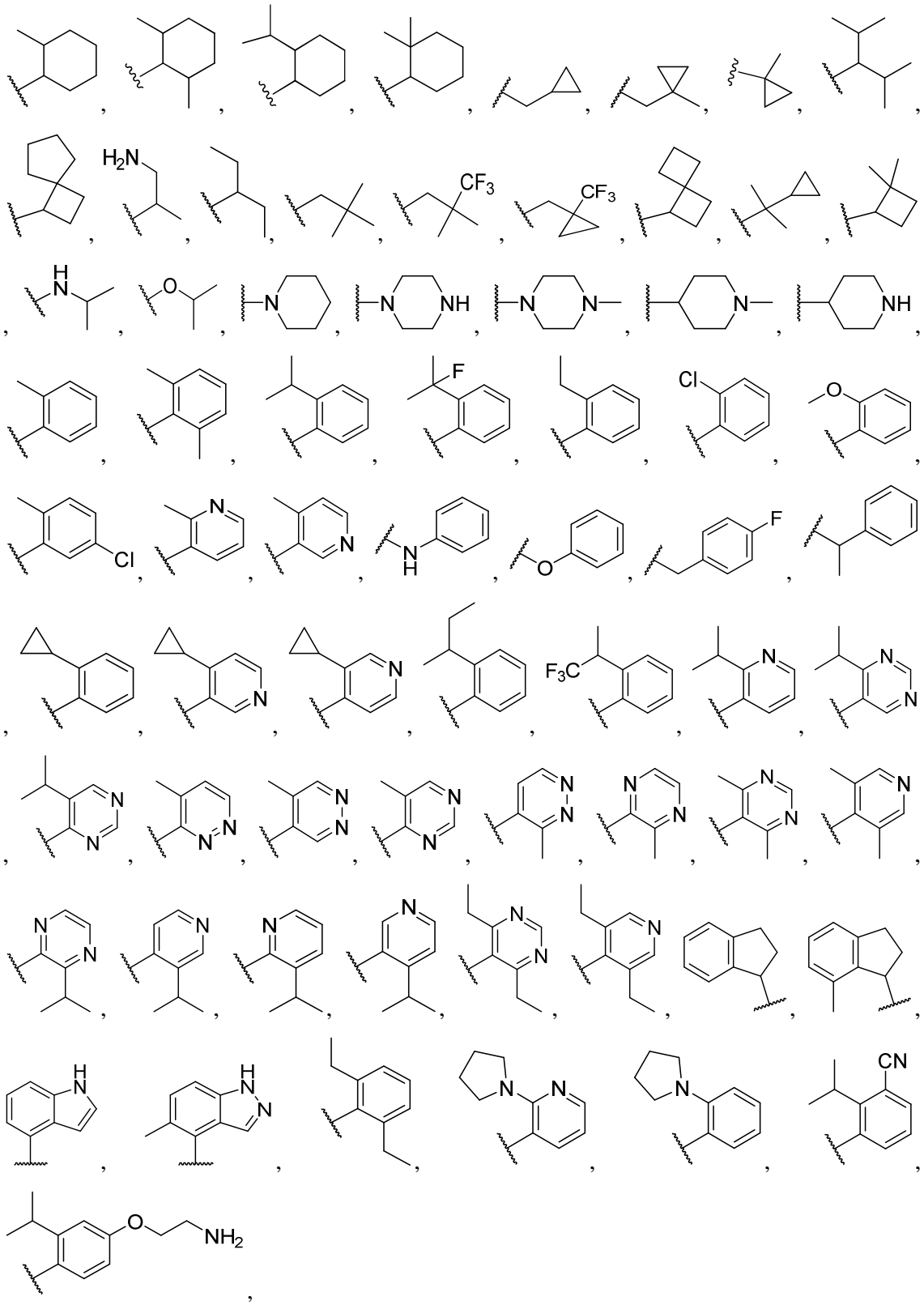
R^7 is H or C_{1-8}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring; and

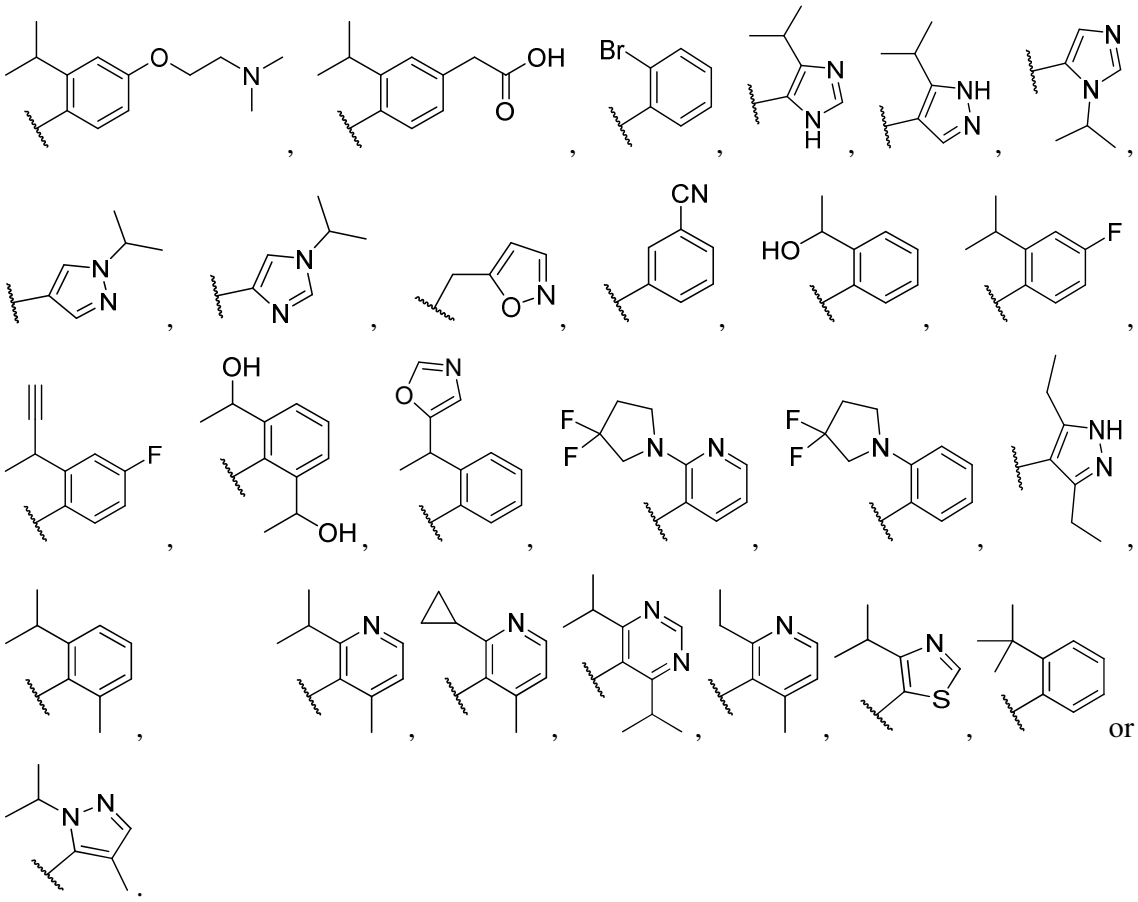
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{3-14}heteroaryl, C_{0-3} alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-C_{3-14}heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, NH-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-3}alkylene-C_{6-14}aryl, NH-C_{0-3}alkylene-C_{2-14}heteroaryl, NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or C_{1-6} alkylene-amine; or a pharmaceutically acceptable salt thereof.

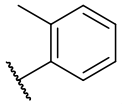
[0020] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some ~~embodiments~~example, each of E^1 and E^2 is CR^1. In other ~~embodiments~~example, E^1 is CR^1 and E^2 is N. In some ~~embodiments~~example, E^1 is N and E^2 is CR^1. In various ~~embodiments~~example, each of E^1 and E^2 is N.

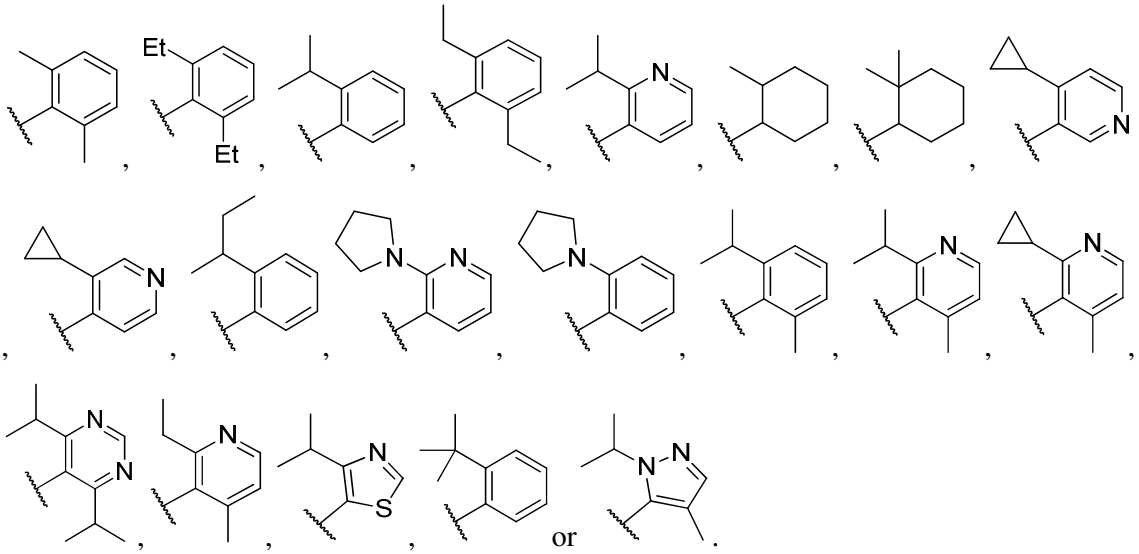
[0021] The compounds of formula (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various ~~embodiments~~example, R^{10} is C_{1-6}alkyl, aryl, heteroaryl, C_{3-14}cycloalkyl, C_{2-14} heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-6}alkylene-C_{6-14}aryl, O-C_{0-6}alkylene-C_{2-14} heteroaryl, O-C_{0-6}alkylene-C_{3-14}cycloalkyl, O-C_{0-6}alkylene-C_{2-14}heterocycloalkyl, N-C_{1-8}alkyl, N(C_{1-8}alkyl)$_2$, NH-C_{0-6}alkylene-C_{6-14}aryl, NH-C_{0-6}alkylene-C_{2-14} heteroaryl, NH-C_{0-6}alkylene-C_{3-14}cycloalkyl, or NH-C_{0-6}alkylene-C_{2-14} heterocycloalkyl. In various ~~embodiments~~example, R^{10} is C_{1-8}alkyl. In some ~~embodiments~~example, R^{10} is C_{0-}

$_3$alkylene-C_{6-14}aryl. In some ~~embodiments~~example, R^{10} is C_{0-3} alkylene-C_{2-14}heteroaryl. In some ~~embodiments~~example, R^{10} is C_{0-3}alkylene-C_{3-14} cycloalkyl. In some ~~embodiments~~example, R^{10} is C_{0-3}alkylene-C_{2-14}heterocycloalkyl. In other ~~embodiments~~example, R^{10} is C_{0-6}alkyleneamine. For example, R^{10} can be *i*-Pr, *t*-Bu, phenyl, benzyl, OCH_3, Cl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

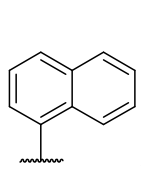
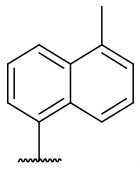
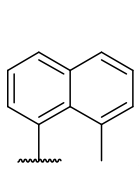
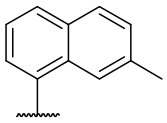
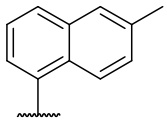
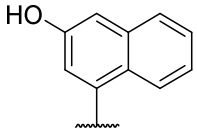
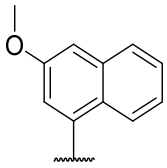
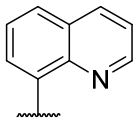
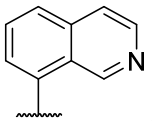
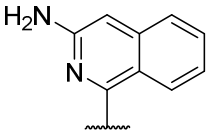
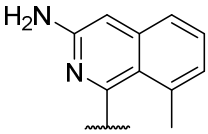
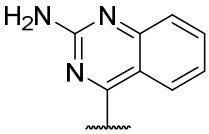
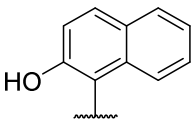
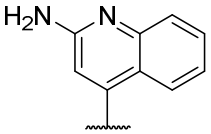
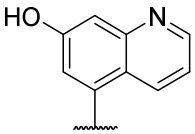
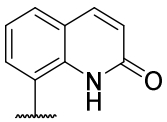
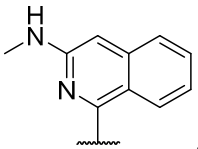
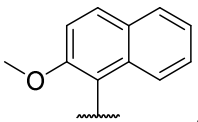
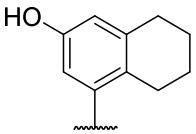
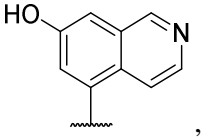
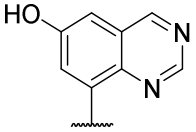
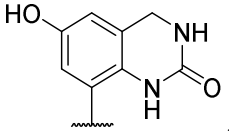
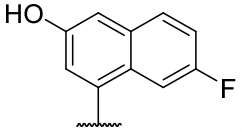
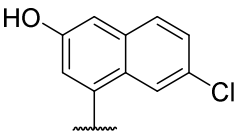
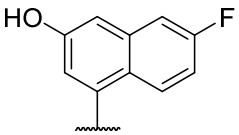
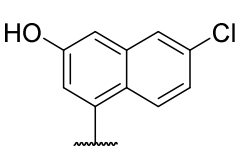
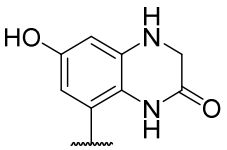
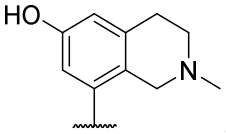
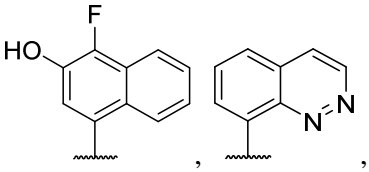


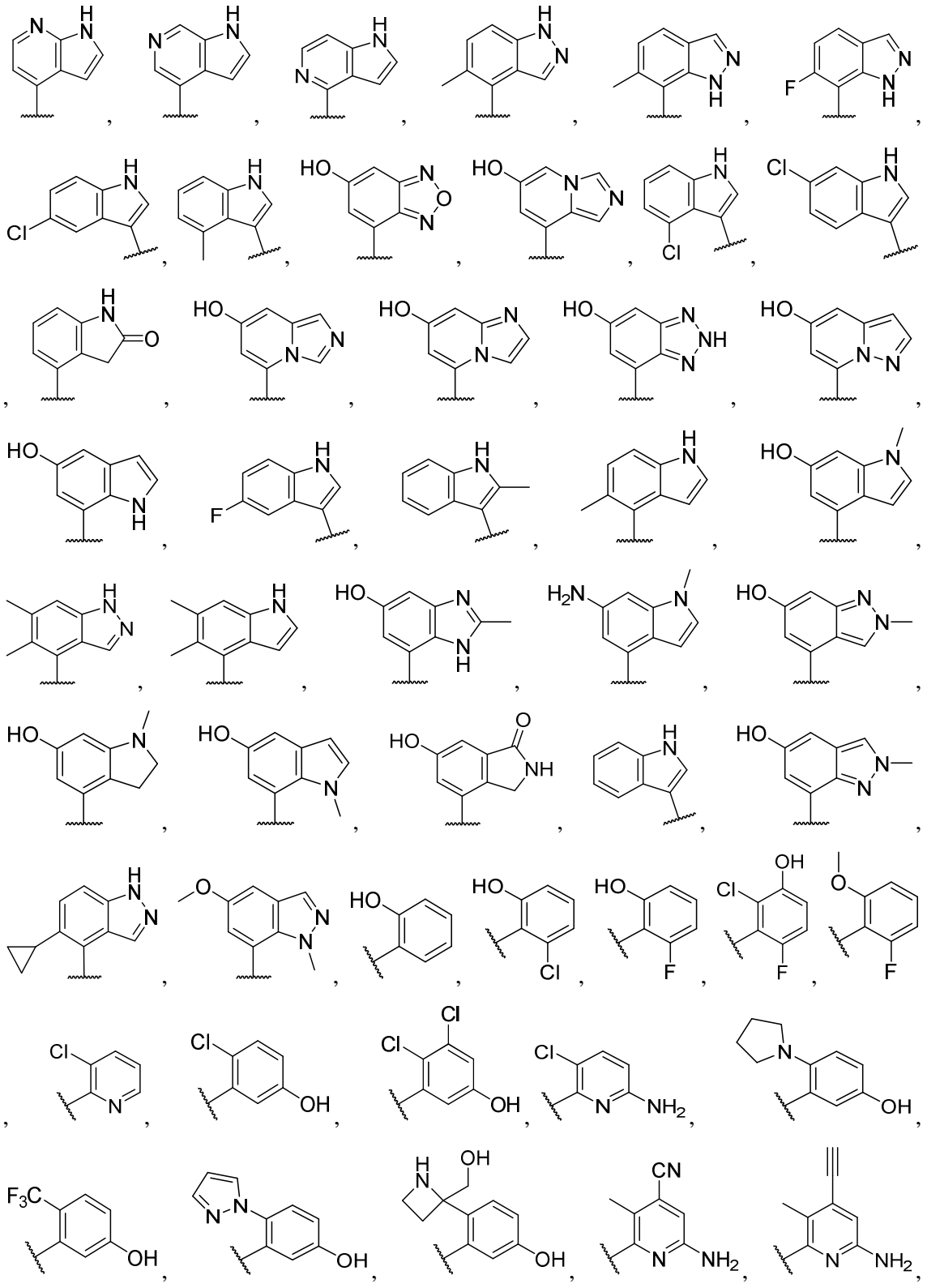


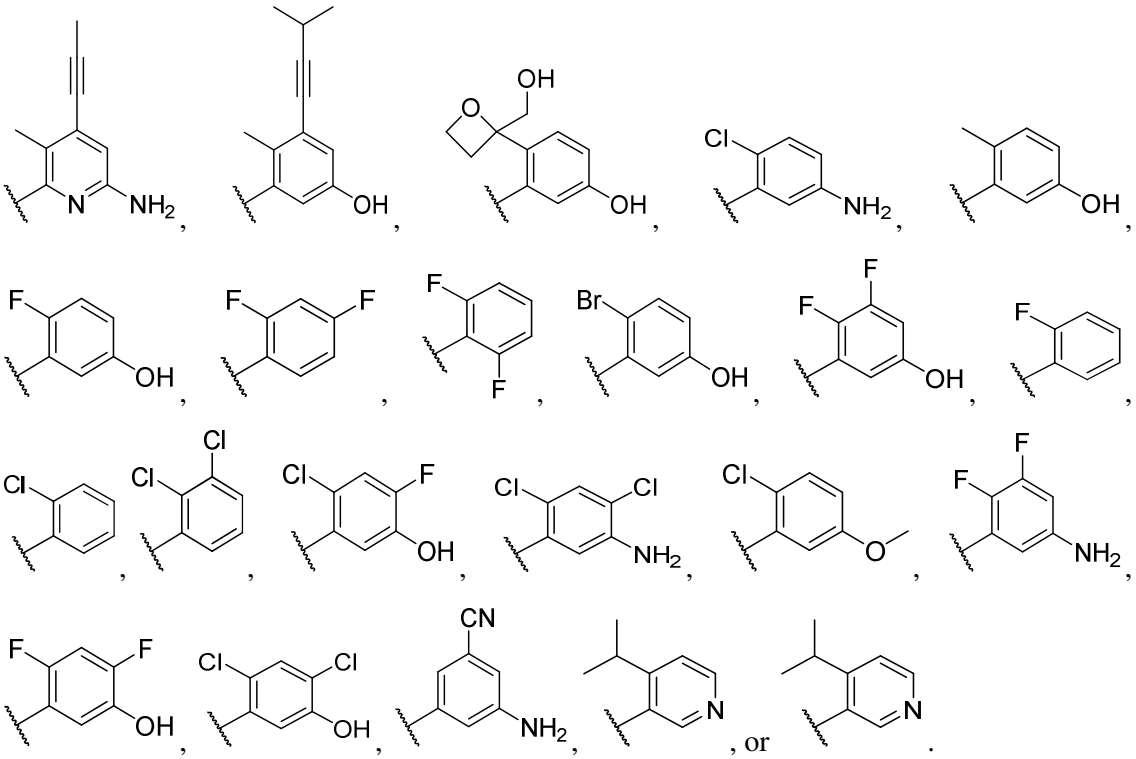
[0022] In some ~~embodiments~~example, R^{10} comprises an ortho-substituted aryl, ortho-substituted heteroaryl, or 2-substituted cyclohexyl. For example, R^{10} can be  ,

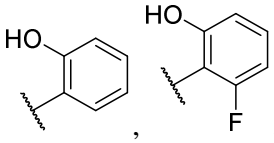


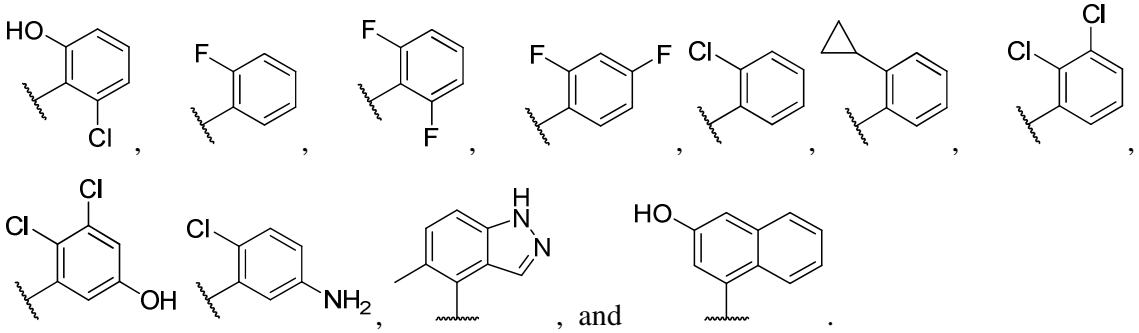
[0023] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some ~~embodiments~~example, R^1 is H. In some ~~embodiments~~example, R^1 is F. In some ~~embodiments~~example, R^1 is methyl.

[0024] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various ~~embodiments~~example, R^2 is aryl. In some ~~embodiments~~example, R^2 is heteroaryl. In various ~~embodiments~~example, R^2 is phenyl, naphthyl, pyridyl, indazolyl, indolyl, azaindolyl, indolinyl, benzotriazolyl, benzoxadiazolyl, imidazolyl, cinnolinyl, imidazopyridyl, pyrazolopyridyl, quinolinyl, isoquinolinyl, quinazolinyl, quinazolinonyl, indolinonyl, isoindolinonyl, tetrahydronaphthyl, tetrahydroquinolinyl, or tetrahydroisoquinolinyl. For example, R^2 can be Cl, Br, CF_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidine, pyrrolidine, azetidine, OCH_3, OCH_2CH_3, phenyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , .



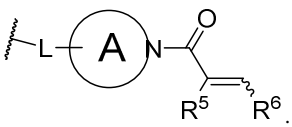
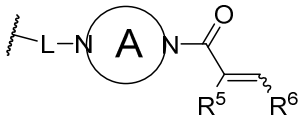
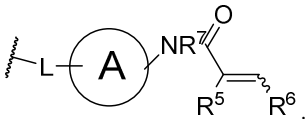
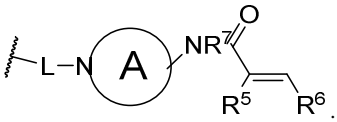
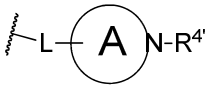
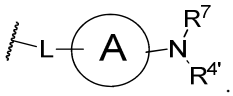
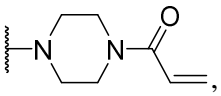
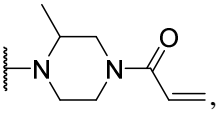
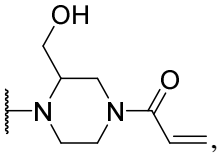


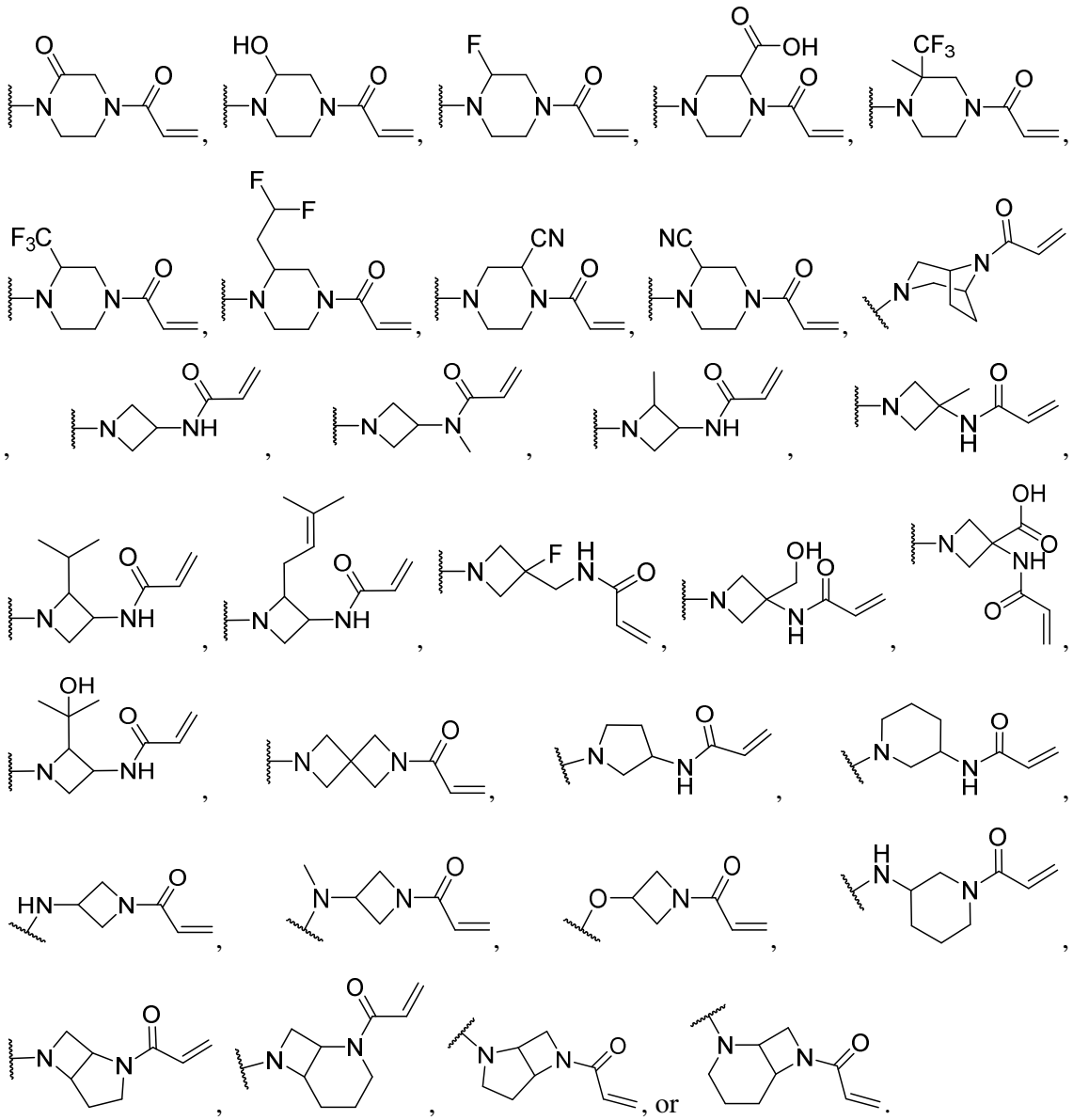
[0025] In various ~~embodiments~~example, R^2 can be bromine, 

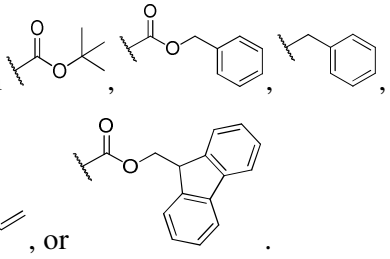


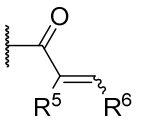
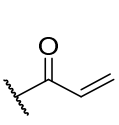
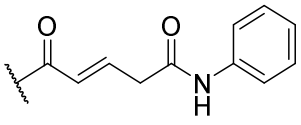
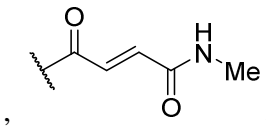
[0026] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various ~~embodiments~~example, R^3 is halo. In various ~~embodiments~~example, R^3 is Cl. In various ~~embodiments~~example, R^3 is F. In some ~~embodiments~~example, R^3 is C_{1-2}alkyl. In some ~~embodiments~~example, R^3 is methyl. In some ~~embodiments~~example, R^3 is C_{1-2}haloalkyl. In various ~~embodiments~~example, R^3 is CF_3.

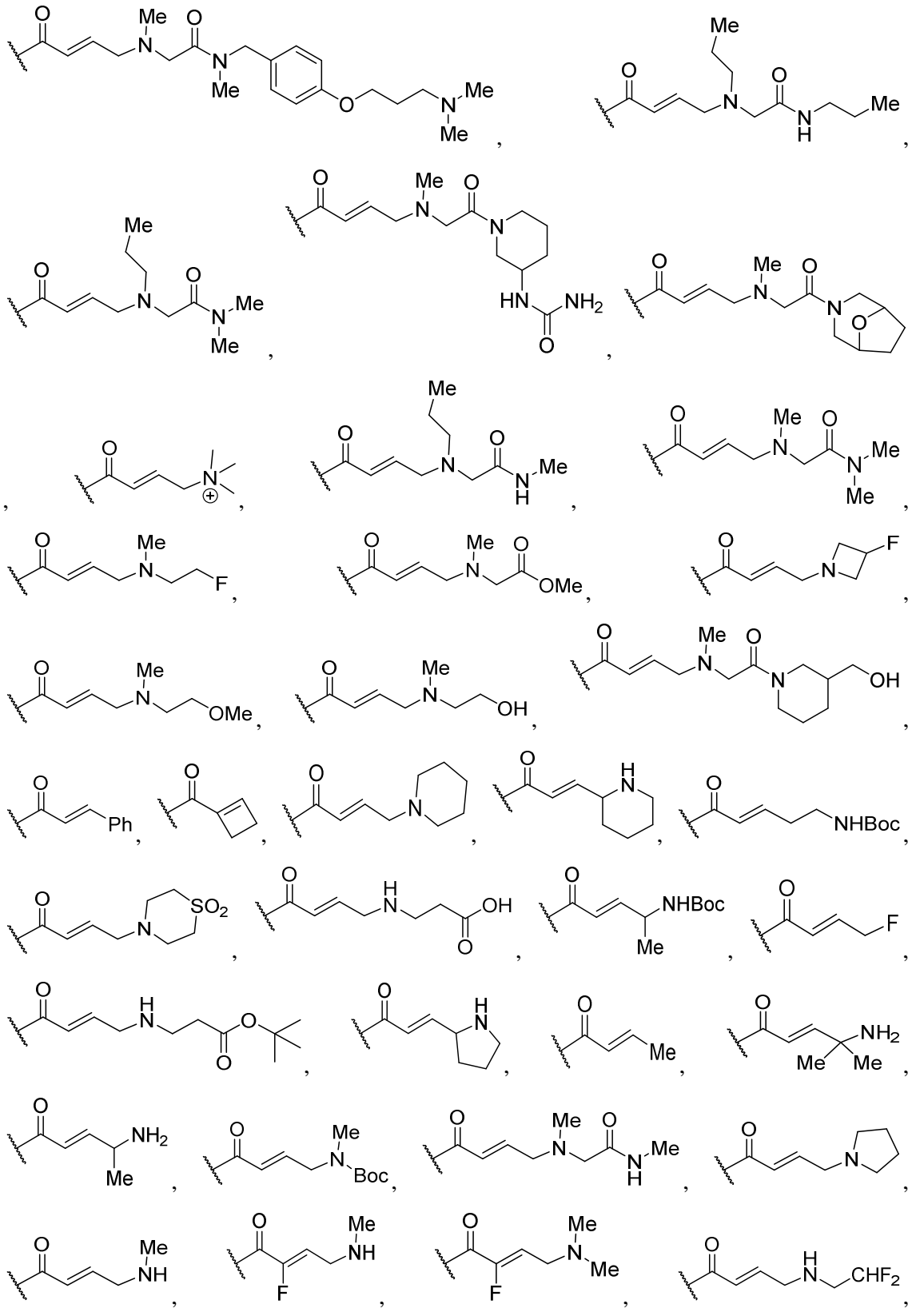
[0027] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some ~~embodiments~~example, R^4 is

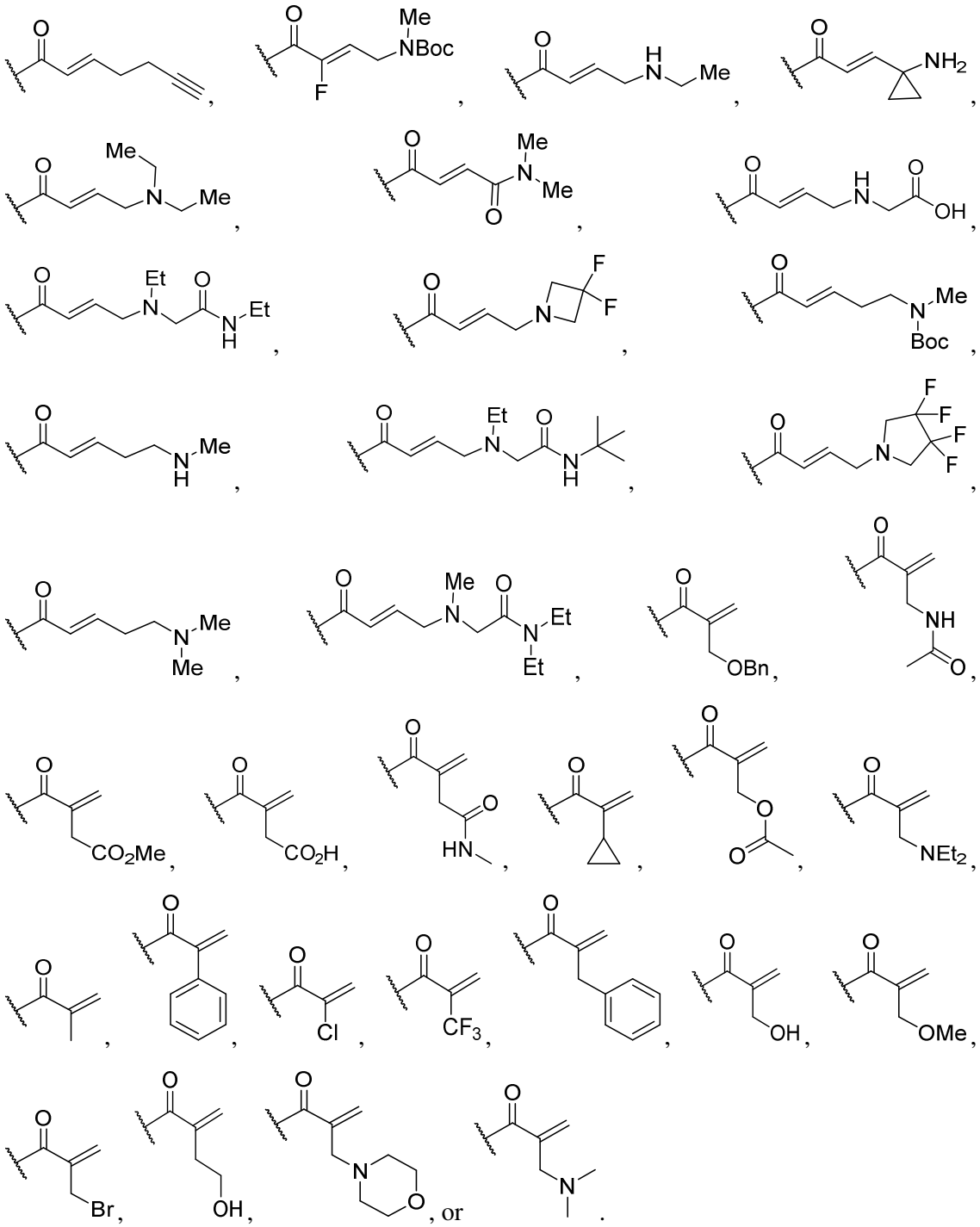
 . In various ~~embodiments~~example, R^4 is  . In some ~~embodiments~~example, R^4 is  . In some ~~embodiments~~example, R^4 is  . In some ~~embodiments~~example, R^4 is  . In some ~~embodiments~~example, R^4 is  . In some ~~embodiments~~example, R^4 can be  ,  ,  ,

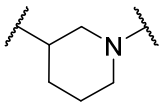
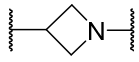


[0028] In various ~~embodiments~~example $R^{4'}$ is H, C_{1-8}alkyl, C_{2-8}alkynyl, C_{1-6}alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{0-3}alkylene-C_{3-8}cycloalkyl, C_{0-3}alkylene-C_{2-7}heterocycloalkyl, C_{0-3}alkylene-C_{6-14}aryl, or selected from 

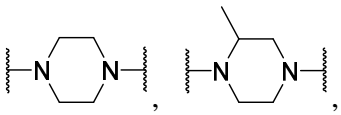
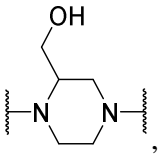
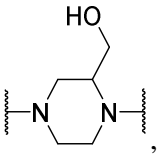
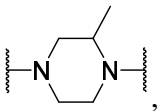
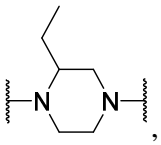
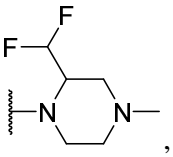
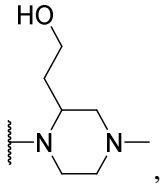
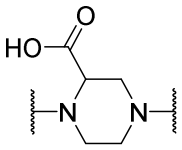
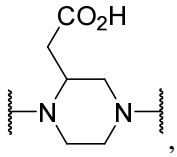
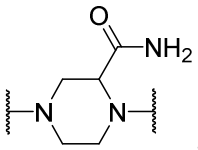
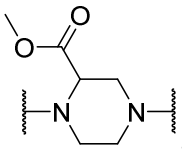
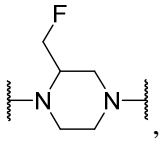
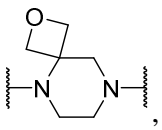
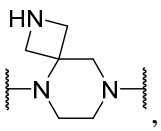
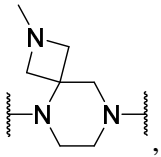
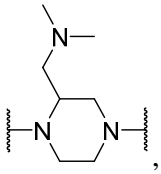
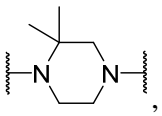
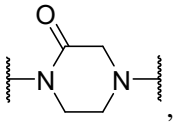
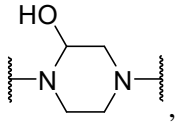
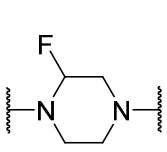
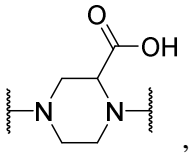
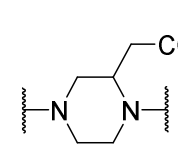
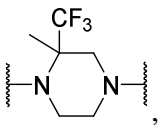
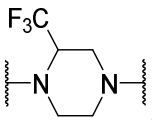
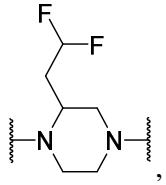
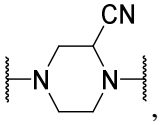
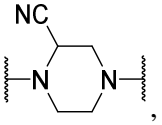
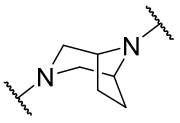
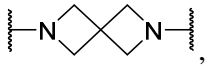
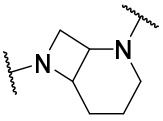
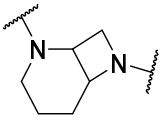
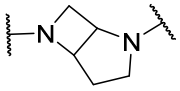
[0029] In various ~~embodiments~~example,  can be  ,  ,  ,

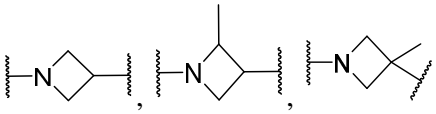
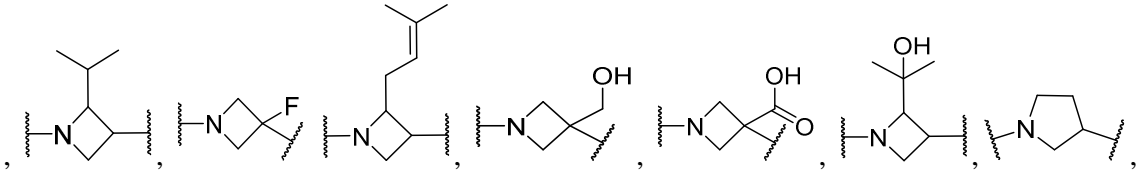
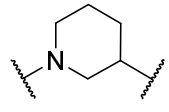




[0030] In some ~~embodiments~~example, ring A is  or  .

[0031] In some ~~embodiments~~example, ring A comprises piperidinyl, piperazinyl, pyrrolidinyl, or azetidinyl. In some ~~embodiments~~example, ring A comprises piperidinyl.

[0032] In various ~~embodiments~~example, ring A can be  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , or  .

[0033] In various ~~embodiments~~example, ring A can be  ,  , or  .

[0034] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features.

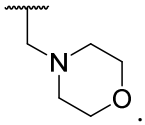
[0035] In some ~~embodiments~~example, L is a bond.

[0036] In some ~~embodiments~~example, L is $C_{1\text{-}2}$alkylene.

[0037] In various ~~embodiments~~example, L is O. In some ~~embodiments~~example, L is S.

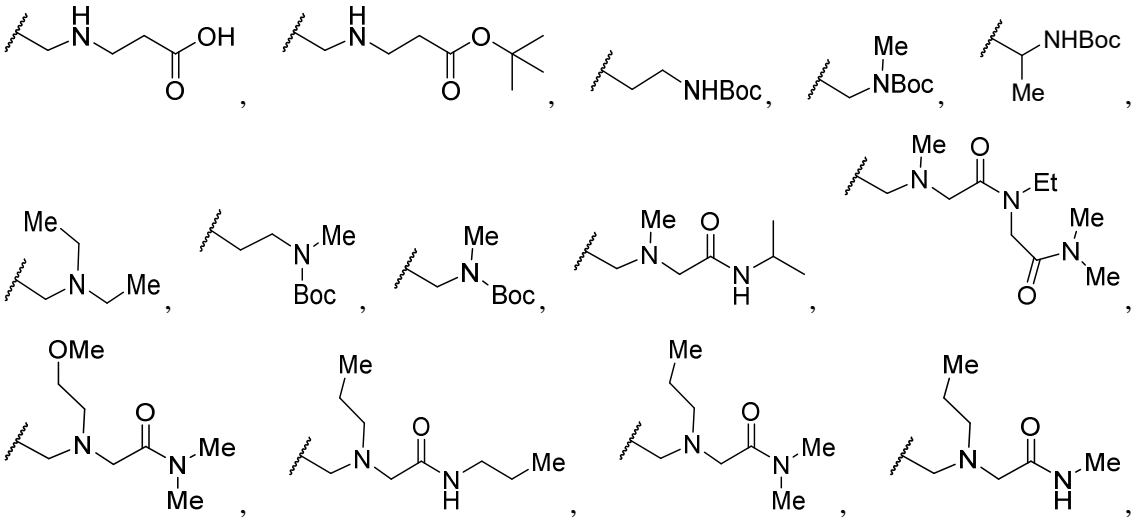
[0038] In various ~~embodiments~~example, L is NH.

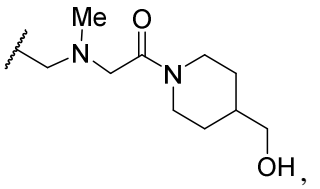
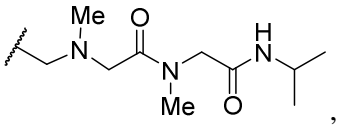
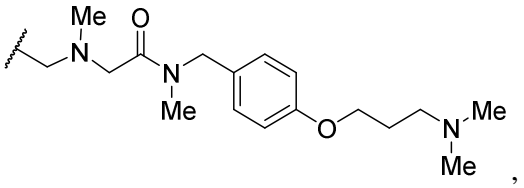
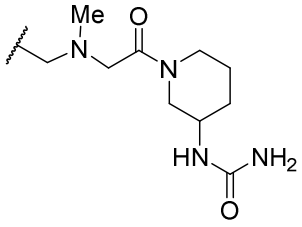
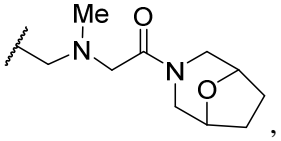
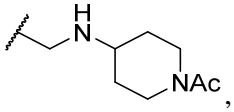
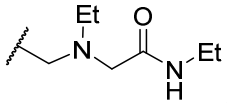
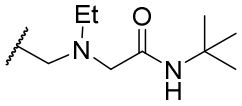
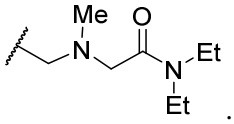
[0039] In some ~~embodiments~~example, R^5 is H or halo.

[0040] In some ~~embodiments~~example, R^5 is H, Br, Cl, F, CN, CH_3, CF_3, CH_2Br, CH_2OH, CH_2CH_2OH, CH_2OCH_2phenyl, cyclopropyl, phenyl, CH_2phenyl, CH_2OCH_3, $CH_2N(CH_3)_2$, $CH_2N(CH_2CH_3)_2$, CH_2CO_2H, $CH_2CO_2CH_3$, $CH_2NHC(O)CH_3$, $CH_2C(O)NHCH_3$, $CH_2OC(O)CH_3$, or  .

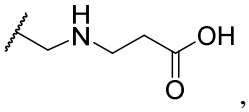
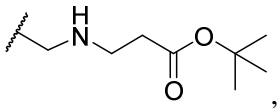
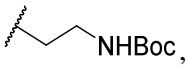
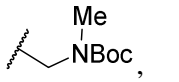
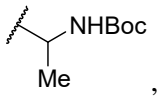
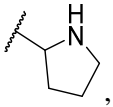
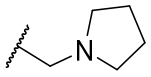
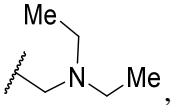
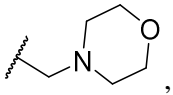
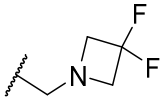
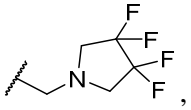
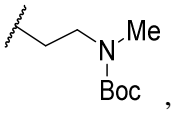
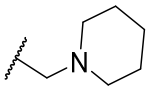
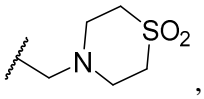
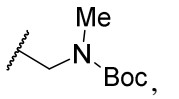
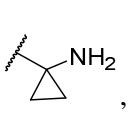
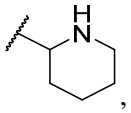
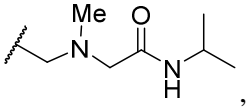
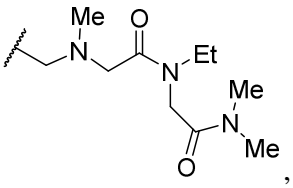
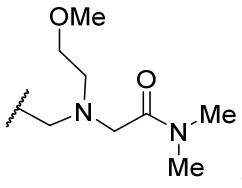
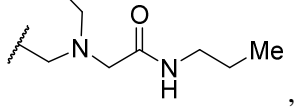
[0041] In some ~~embodiments~~example, R^6 is $C_{1\text{–}6}$alkyl, $C_{1\text{–}6}$alkylene-O-$C_{1\text{-}6}$alkyl, $C_{1\text{–}6}$alkylene-OH, $C_{1\text{–}3}$haloalkyl, $C_{1\text{–}6}$alkylene-amine, $C_{0\text{–}6}$alkylene-amide, $C_{0\text{–}1}$alkylene C(O)O$C_{1\text{-}3}$alkyl, $C_{0\text{–}1}$alkylene-$C_{2\text{-}14}$heterocycloalkyl, $C_{0\text{–}1}$alkylene-$C_{3\text{-}14}$cycloalkyl, or $C_{0\text{–}3}$alkylene-$C_{6\text{-}14}$aryl.

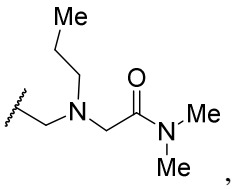
[0042] In various ~~embodiments~~example, R^6 is $C_{0\text{–}6}$alkylene-amine or $C_{0\text{–}3}$alkylene-amide and is CH_2NH_2, $CH(CH_3)NH_2$, $CH(CH_3)_2NH_2$, $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, CH_2NHCH_3, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $CH_2C(O)NH$phenyl, $CH_2NHC(O)CH_3$, $CH_2NHCH_2CH_2OH$, $CH_2NHCH_2CO_2H$, $CH_2NH(CH_3)CH_2CO_2CH_3$,$CH_2NHCH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2C(O)N(CH_3)_2$, $CH_2NH(CH_3)CH_2C(O)NHCH_3$, CH_2NMe_2, $CH_2NH(CH_3)CH_2CH_2OH$, $CH_2NH(CH_3)CH_2CH_2F$, $CH_2N^+(CH_3)_3$, $CH_2NHCH_2CHF_2$, $CH_2NHCH_2CH_3$,



[0043] In various ~~embodiments~~example, R^6 is phenyl, cyclopropyl, CH_3, CF_3, CH_2CH_3, CH_2NH_2, $CH(CH_3)NH_2$, $CH(CH_3)_2NH_2$, CH_2Cl, CH_2Br, CH_2OCH_3, CH_2Ophenyl, CH_2OH, CO_2H, $CO_2CH_2CH_3$, CH_2CO_2H, $CH_2CH_2NH_2$, CH_2CH_2OH, $CH_2CH_2N(CH_3)_2$, CH_2NHCH_3, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $CH_2C(O)NH$phenyl, CH_2CHF_2, CH_2F, CHF_2, $CH_2NHC(O)CH_3$, $CH_2NHCH_2CH_2OH$, $CH_2NHCH_2CO_2H$, $CH_2NH(CH_3)CH_2CO_2CH_3$,$CH_2NHCH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2C(O)N(CH_3)_2$, $CH_2NH(CH_3)CH_2C(O)NHCH_3$, CH_2CH_2CCH, CH_2NMe_2, $CH_2NH(CH_3)CH_2CH_2OH$, $CH_2NH(CH_3)CH_2CH_2F$, $CH_2N^+(CH_3)_3$, $CH_2NHCH_2CHF_2$, $CH_2NHCH_2CH_3$,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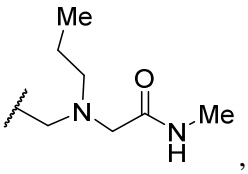
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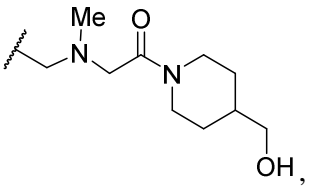
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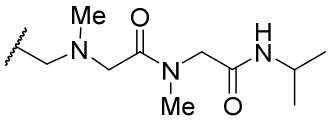
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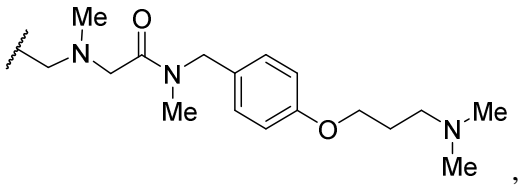
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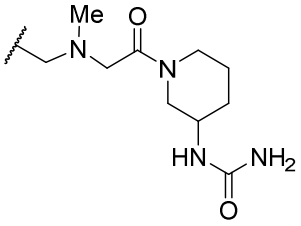
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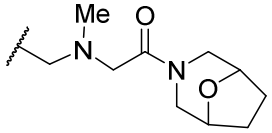
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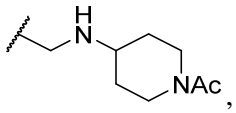
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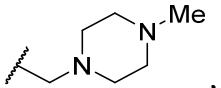
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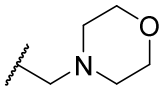
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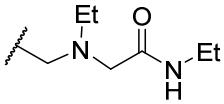
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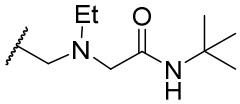
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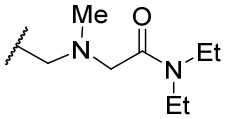
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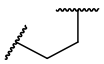
[0044] In various ~~embodiments~~example, R^5 and R^6 together are 
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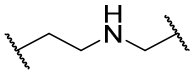
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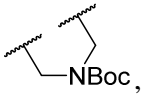
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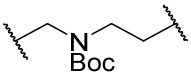
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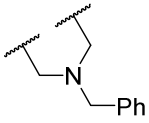
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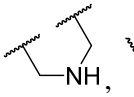
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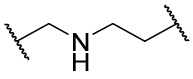
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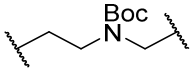
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[0045] In some ~~embodiments~~example, each of R^5 and R^6 is H.

[0046] In some ~~embodiments~~example, R^7 is H.

[0047] In some ~~embodiments~~example, R^7 is methyl.

[0048] In various ~~embodiments~~example, R^7 and R^5 together are $–CH_2–$ or $–C(O)CH_2–$.

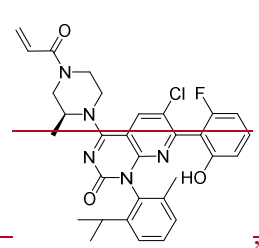
[0049] The compounds disclosed herein can be in the form of a pharmaceutically acceptable salt. The compounds provided can be formulated into a pharmaceutical formulation comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

[0050] Also provided is a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with a compound or composition disclosed herein. Further provided is a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound or composition disclosed herein. In some ~~embodiments~~example, the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

CLAIMS

What is claimed is:

~~1. A compound having a structure selected from:~~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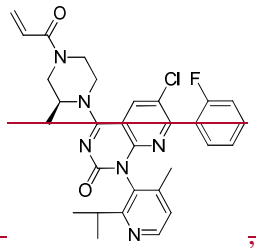
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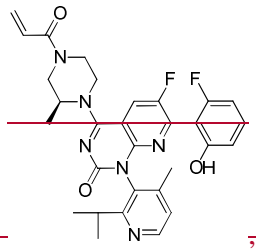
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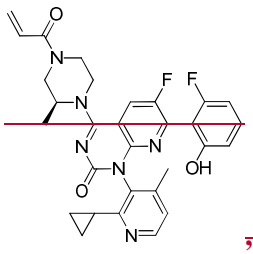
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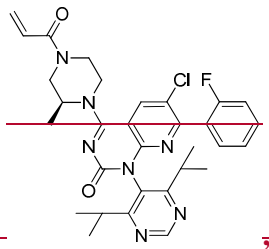
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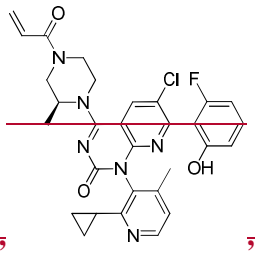
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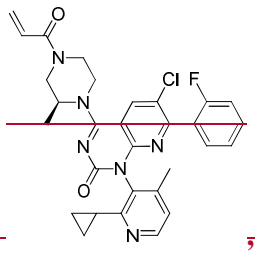
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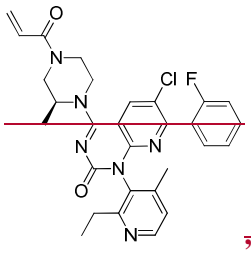
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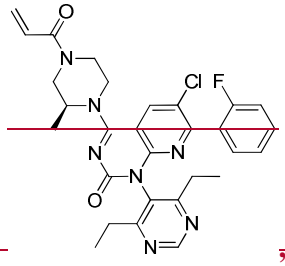
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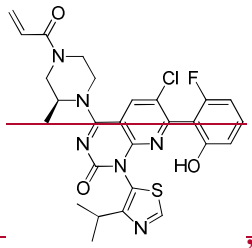
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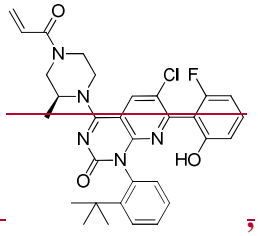
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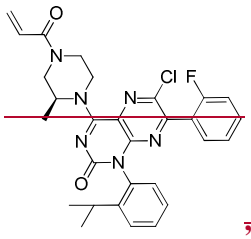
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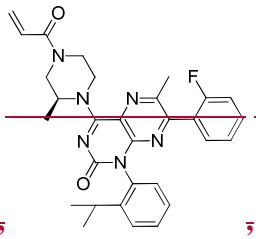
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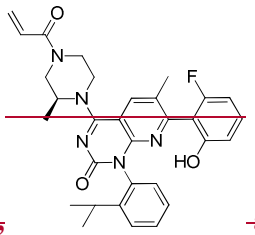
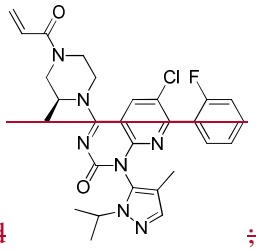
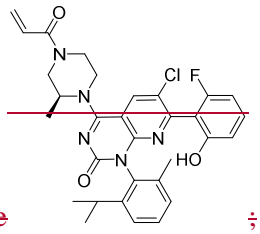
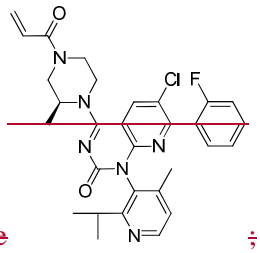

~~and~~

~~;~~

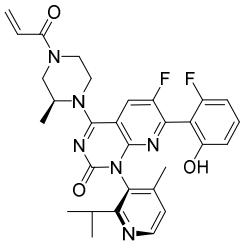
~~or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.~~

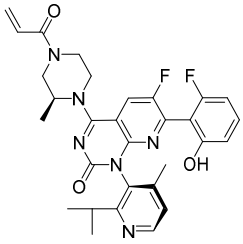
~~2. A compound having a structure~~  ~~;~~

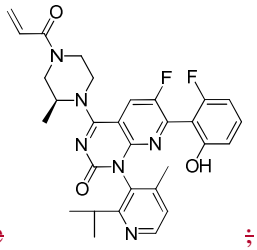
~~or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.~~

~~3. A compound having a structure~~  ~~;~~

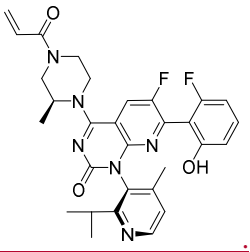
~~or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.~~

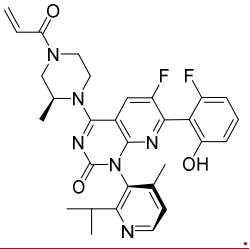
1. A compound, wherein the compound is  or a pharmaceutically acceptable salt thereof.

2. A compound, wherein the compound is  or a pharmaceutically acceptable salt thereof.

43. A compound wherein the compound is ~~having a structure~~  ~~;~~

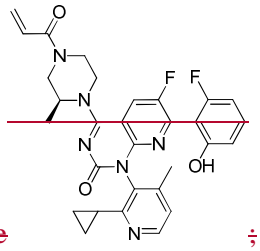
~~or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof~~.

4. A compound, wherein the compound is  .

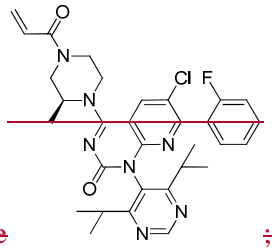
5. A compound, wherein the compound is  .

6. Atropisomer 1 of the compound of claim 3, corresponding to the 1st-eluting isomer obtainable by separating the atropoisomers with supercritical fluid chromatography applying Chiralpak IC, 30x250 mm, 5 µm, 55%MeOH/CO_2, 120 g/min, 10.3 MPa (103 bar).

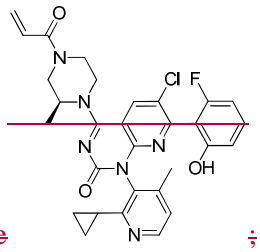
7. Atropisomer 2 of the compound of claim 3, corresponding to the 2nd-eluting isomer obtainable by separating the atropoisomers with supercritical fluid chromatography applying Chiralpak IC, 30x250 mm, 5 µm, 55%MeOH/CO_2, 120 g/min, 10.3 MPa (103 bar).

5. A compound having a structure  ;

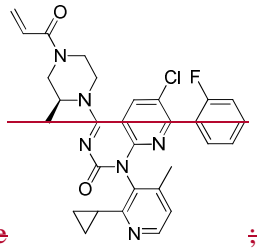
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

6. A compound having a structure  ;

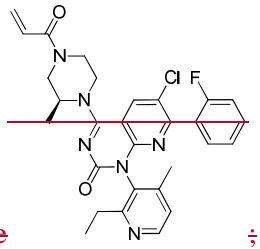
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

7. A compound having a structure  ;

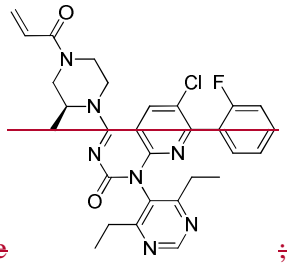
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

8. A compound having a structure  ;

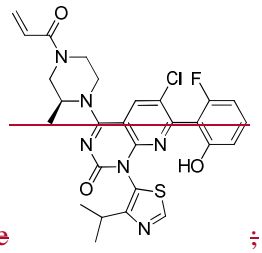
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

9. A compound having a structure  ;

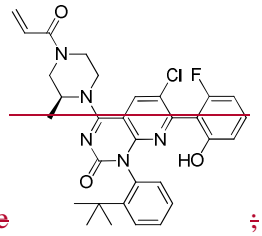
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

10. A compound having a structure  ;

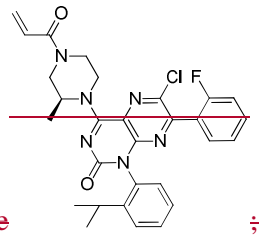
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

11. A compound having a structure  ;

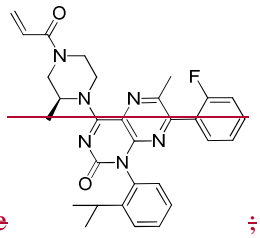
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

12. A compound having a structure  ;

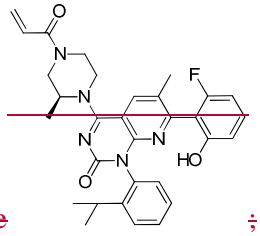
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

13. A compound having a structure  ;

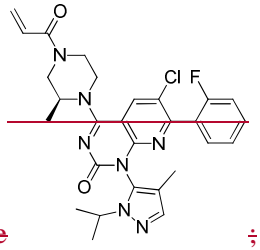
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

~~14. A compound having a structure~~  ~~;~~

~~or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.~~

~~15. A compound having a structure~~  ~~;~~

~~or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.~~

~~16. A compound having a structure~~  ~~;~~

~~or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.~~

~~17. The compounds of any one of claims 1-16 in the form of a pharmaceutically acceptable salt.~~

~~1~~8. A pharmaceutical ~~formulation~~ composition comprising ~~any one or more of~~ the compound~~s of~~ according to any one of claims 1-~~1~~7 and a pharmaceutically acceptable excipient.

~~1~~9. An *in vitro* method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 1-~~1~~7 or the composition of claim ~~1~~8.

~~20. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-17 or the composition of claim 18.~~

~~21. The method of claim 20, wherein the cancer is lung cancer, pancreatic cancer, or colorectal cancer.~~

~~22. The method of claim 20, wherein the cancer is lung cancer.~~

~~23. The method of claim 20, wherein the cancer is pancreatic cancer.~~

~~24. The method of claim 20, wherein the cancer is colorectal cancer.~~

~~25. The method of claim 20, further comprising administering to the patient in need thereof a therapeutically effective amount of an additional pharmaceutically active compound.~~

~~26. The method of claim 25, wherein the additional pharmaceutically active compound is carfilzomib.~~

~~27. The method of claim 25, wherein the additional pharmaceutically active compound is cytarabine.~~

~~28. Use of a compound according to any one of Claims 1-18 for treating cancer in a subject.~~

~~29. A compound according to any one of Claims 1-16 in the preparation of a medicament for treating cancer.~~

~~30. The compound according to Claim 29, wherein the cancer is a hematologic malignancy.~~

~~31~~10. Use of the compound ~~A compound according to~~ of any one of Claims 1-~~16~~ 7 in the manufacture of a medicament for treating cancer in a subject~~for treating cancer~~.

~~32. The compound according to Claim 31, wherein the cancer is a hematologic malignancy.~~

11. The use of claim 10, wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, liver cancer, small cell lung cancer, cervical cancer, a germ cell tumor, ovarian cancer, a pancreatic neuroendocrine tumor, bladder cancer, myelodysplastic or myeloproliferative neoplasms, head and neck cancer, esophageal cancer, soft tissue sarcoma, malignant mesothelioma, thyroid cancer, leukemia, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

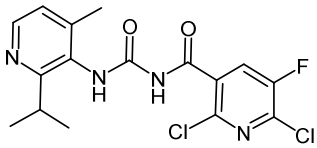
12. The use of claim 10, wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

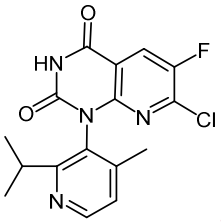
13. The use of claim 12, wherein cancer is non-small cell lung cancer.

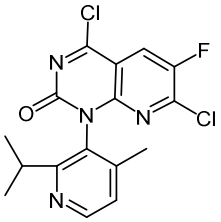
14. The compound for use according to claim 12, wherein the cancer is colorectal cancer.

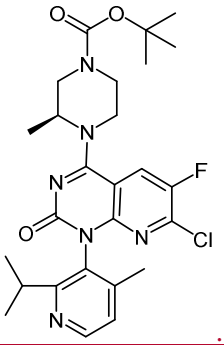
15. The compound for use according to claim 12, wherein the cancer is pancreatic cancer.

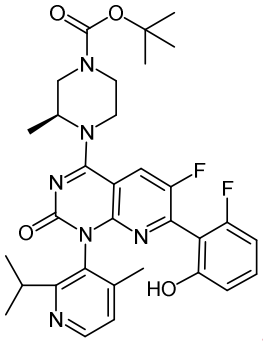
16. The compound for use according to any one of claims 12-15, wherein the cancer is mediated by a KRAS G12C mutation.

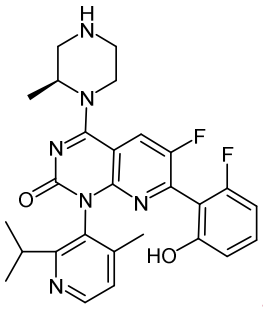
17. A compound, wherein the compound is  .

18. A compound, wherein the compound is  .

19. A compound, wherein the compound is  .

20. A compound, wherein the compound is  .

21. A compound, wherein the compound is  .

22. A compound, wherein the compound is  .

23. A process for preparing a compound of any one of claims 1-7, comprising providing a compound according to any one claims 17-22 and converting it into a compound of any one of claims 1-7.