KRAS G12C INHIBITORS AND METHODS OF USING THE SAME

FIELD OF INVENTION

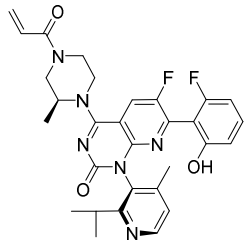
[0001] Provided herein are KRAS G12C inhibitors, composition of the same, and methods of using the same. These inhibitors are useful for treating a number of disorders, including pancreatic, colorectal, and lung cancers.

BACKGROUND

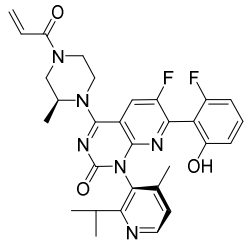
[0002] KRAS gene mutations are common in pancreatic cancer, lung adenocarcinoma, colorectal cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. KRAS mutations are also observed in about 25% of patients with NSCLC, and some studies have indicated that KRAS mutations are a negative prognostic 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

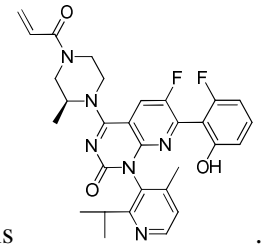
[0002a] In one aspect, the present disclosure provides

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

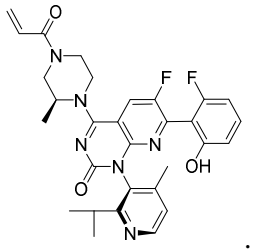
[0002b] In one aspect, the present disclosure provides

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

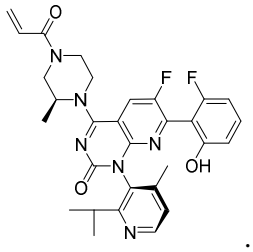
[0002c] In one aspect, the present disclosure provides

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

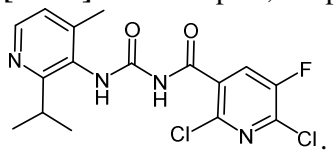
a compound, wherein the compound is  .

[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.

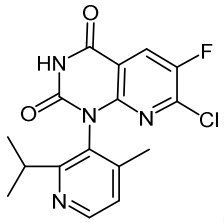
[0002h] In one aspect, the present disclosure provides a use of the compound of the disclosure in the manufacture of a medicament for treating cancer in a subject.

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



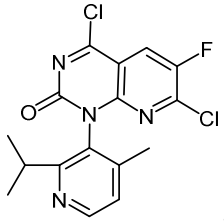
.

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



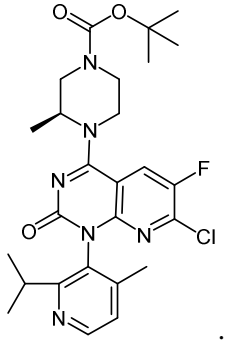
.

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



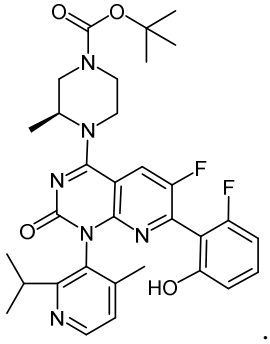
.

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



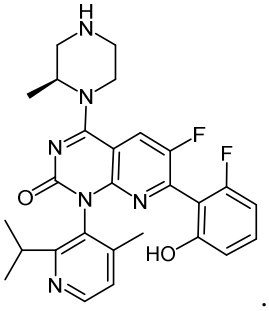
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[0002m] In one aspect, the present disclosure provides a compound, wherein the compound is



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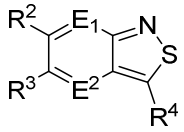
[0002n] In one aspect, the present disclosure provides a compound, wherein the compound is



.

[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

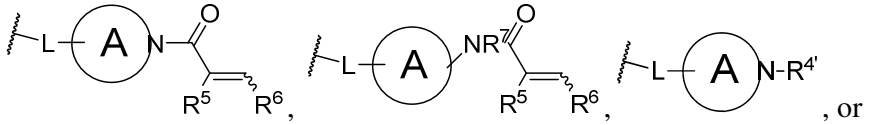
E^1 and E^2 are each independently N or CR^1;

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;

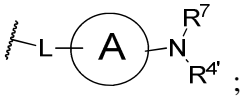
R^2 is halo, $C_{1–6}$alkyl, $C_{1–6}$haloalkyl, OR', N(R')$_2$, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, $C_{0–3}$ alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, $C_{0–3}$ alkylenearyl, or $C_{0–3}$ alkyleneheteroaryl, and each R' is independently H, C_{1-6} 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

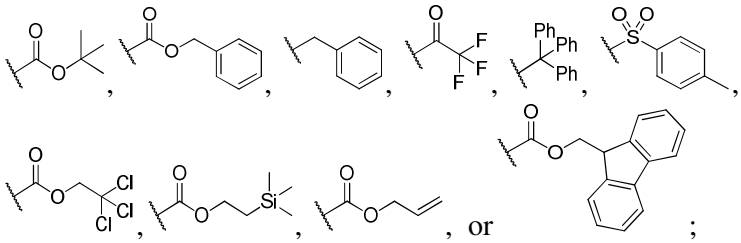


;

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



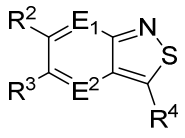
, or ;

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 example, provided herein are compounds having a structure of formula (I)



(I)

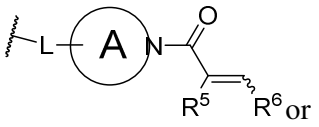
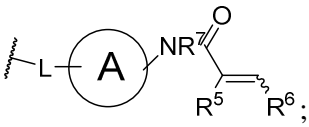
wherein

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;

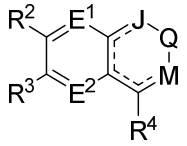
L is a bond, C_{1-6}alkylene, -O-$C_{0–5}$alkylene, -S-$C_{0–5}$alkylene, or -NH-$C_{0–5}$ alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

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

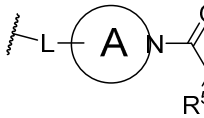
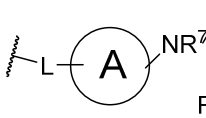
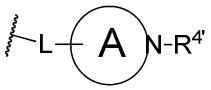
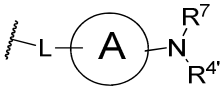
R^7 is H or $C_{1–6}$alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring,

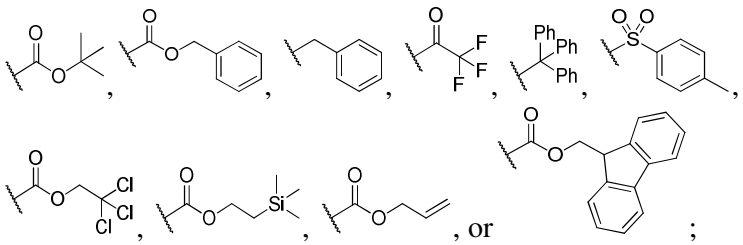
or a pharmaceutically acceptable salt thereof.

[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};

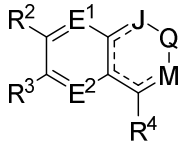
(2) when M is NR^{13}, J is N or CR^{10};

(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 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 examples, J is NR^{10} and M is CR^{13}. In some examples, J is CR^{10} and M is NR^{13}. In some examples, J is N and M is NR^{13}. In various 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};

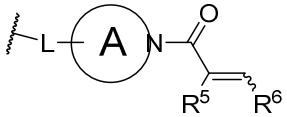
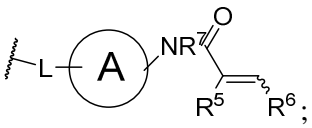
M is N, NR^{13}, or CR^{13};

--- 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};

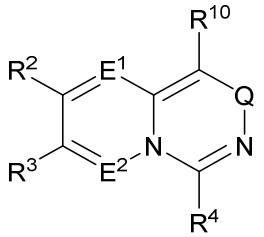
(2) when M is NR^{13}, J is N or CR^{10};

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

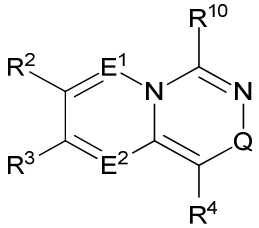
(4) when M is CR^{13}, J is N or NR^{10}.

[0008] In some 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 examples, J is NR^{10} and M is CR^{13}. In some examples, J is CR^{10} and M is NR^{13}. In some examples, J is N and M is NR^{13}. In various 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



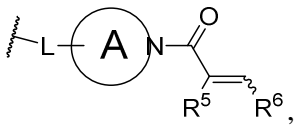
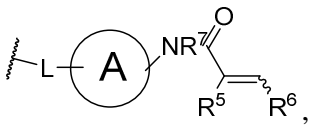
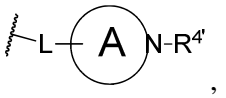
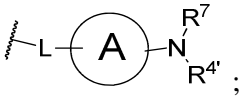
(III'),

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;

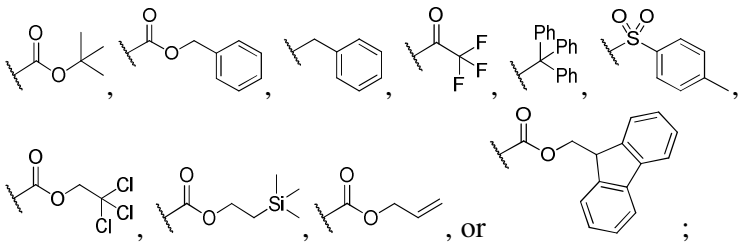
R^3 is halo, C_{1-3}alkyl, C_{1-2}haloalkyl, C_{1-3}alkoxy, C_{3-4}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3} alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl;

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;

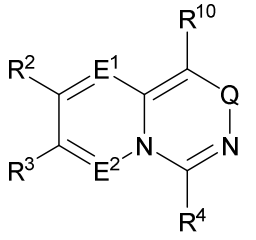
Q is CR^8R^9, $C{=}CR^8R^9$, C=O, C=S, or $C{=}NR^8$;

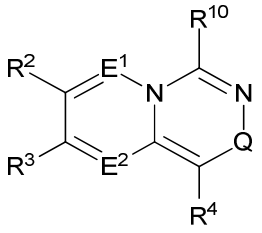
R^8 and R^9 are each independently H, $C_{1–6}$alkyl, hydroxy, $C_{1–6}$alkoxy, cyano, nitro, or $C_{3–14}$cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

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')

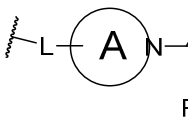
wherein

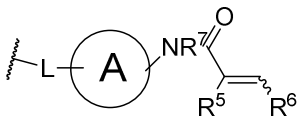
E^1 and E^2 are each independently N or CR^1;

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 $C=NR^8$;

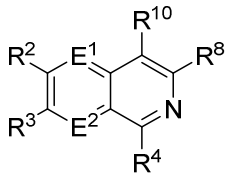
R^8 and R^9 are each independently H, $C_{1–6}$alkyl, hydroxy, $C_{1–6}$alkoxy, cyano, nitro, or $C_{3–14}$cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

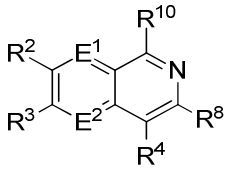
R^{10} is $C_{1–8}$alkyl, $C_{0–3}$alkylene-C_{6-14}aryl, $C_{0–3}$alkylene-$C_{3–14}$heteroaryl, $C_{0–3}$ alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{1–6}$alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-$C_{3–14}$heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, 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 examples, the compouds have a structure of formula (III). In other 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 examples, Q is C=O. In some examples, Q is C=S. In some examples, Q is $C=NR^8$. In various examples, R^8 is C_{1-2}alkyl. In some examples, Q is CR^8R^9. In various examples, Q is $C=CR^8R^9$. In some 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 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


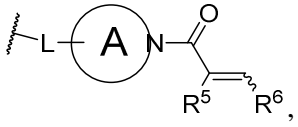
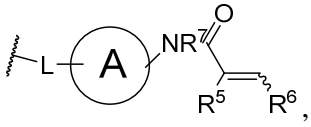
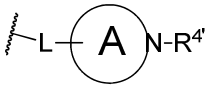
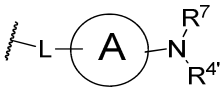
(IV') E^1 and E^2 are each independently CR^1 or N;

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;

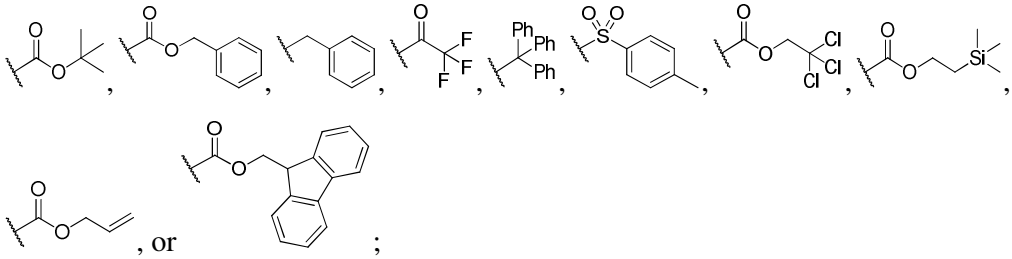
R^3 is halo, $C_{1–2}$haloalkyl, $C_{1–3}$alkoxy, $C_{3–4}$cycloalkyl, $C_{2–3}$alkenyl, $C_{2–3}$alkynyl, aryl, or heteroaryl;

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 $NR^{11}R^{12}$;

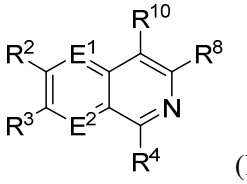
R^{11} and R^{12} are each independently H, $C_{1–8}$alkyl, or $C_{3–14}$cycloalkyl; and

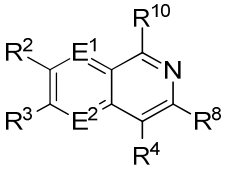
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-$C_{2–14}$heteroaryl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, $C_{1–6}$alkoxy, O-C_{0-3}alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-$C_{2–14}$heteroaryl, O-C_{0-3}alkylene-C_{3-14} cycloalkyl, O-C_{0-3}alkylene-C_{2-14}heterocycloalkyl,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

[0014] In some examples, the compouds disclosed herein have a structure of formula (IV). In various examples, the compouds disclosed herein have a structure of formula (IV'). In some 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 examples, R^8 is methyl.

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



(IV) or


(IV')

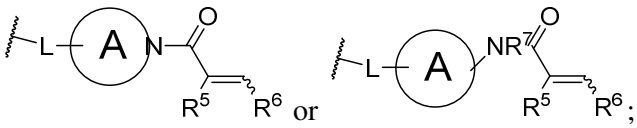
wherein

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

R^1 is independently H, hydroxy, C_{1-6}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, $C_{1–2}$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, $C_{1\text{-}6}$alkylene, -O-$C_{0\text{-}5}$alkylene, -S-$C_{0\text{-}5}$alkylene, or -NH-$C_{0\text{-}5}$ 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^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 $C_{3–15}$cycloalkyl; and

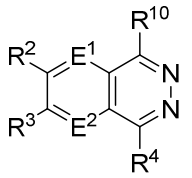
R^{10} is $C_{1–8}$alkyl, $C_{0–3}$alkylene-$C_{6\text{-}14}$aryl, $C_{0–3}$alkylene-$C_{3–14}$heteroaryl, $C_{0–3}$ alkylene-$C_{3–14}$cycloalkyl, $C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, $C_{1–6}$alkoxy, O-$C_{0\text{-}3}$ alkylene-$C_{6\text{-}14}$aryl, O-$C_{0\text{-}3}$alkylene-$C_{3–14}$heteroaryl,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

or a pharmaceutically acceptable salt thereof.

[0016] In some example, the compouds disclosed herein have a structure of formula (IV). In various example, the compouds disclosed herein have a structure of formula (IV'). In some 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 example, R^8 is methyl.

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



(V)

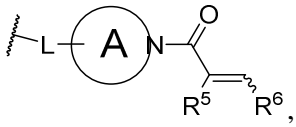
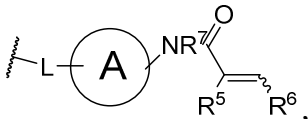
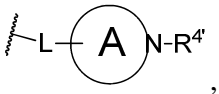
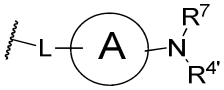
wherein

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;

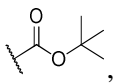
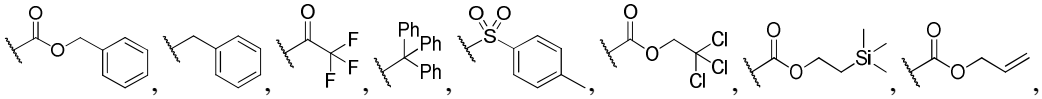
R^2 is halo, C_{1-6}alkyl, C_{1-6}haloalkyl, OR', N(R')$_2$, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or C_{0-3}alkylene-C_{2-14}heteroaryl, and each R' is independently H, C_{1-6}alkyl, 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;

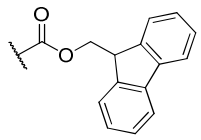
R^3 is halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-14}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, or heteroaryl;

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

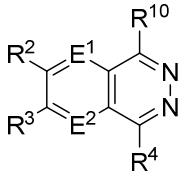

;

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)

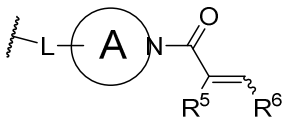
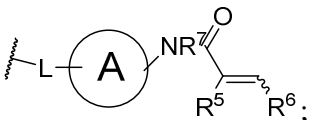
wherein

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;

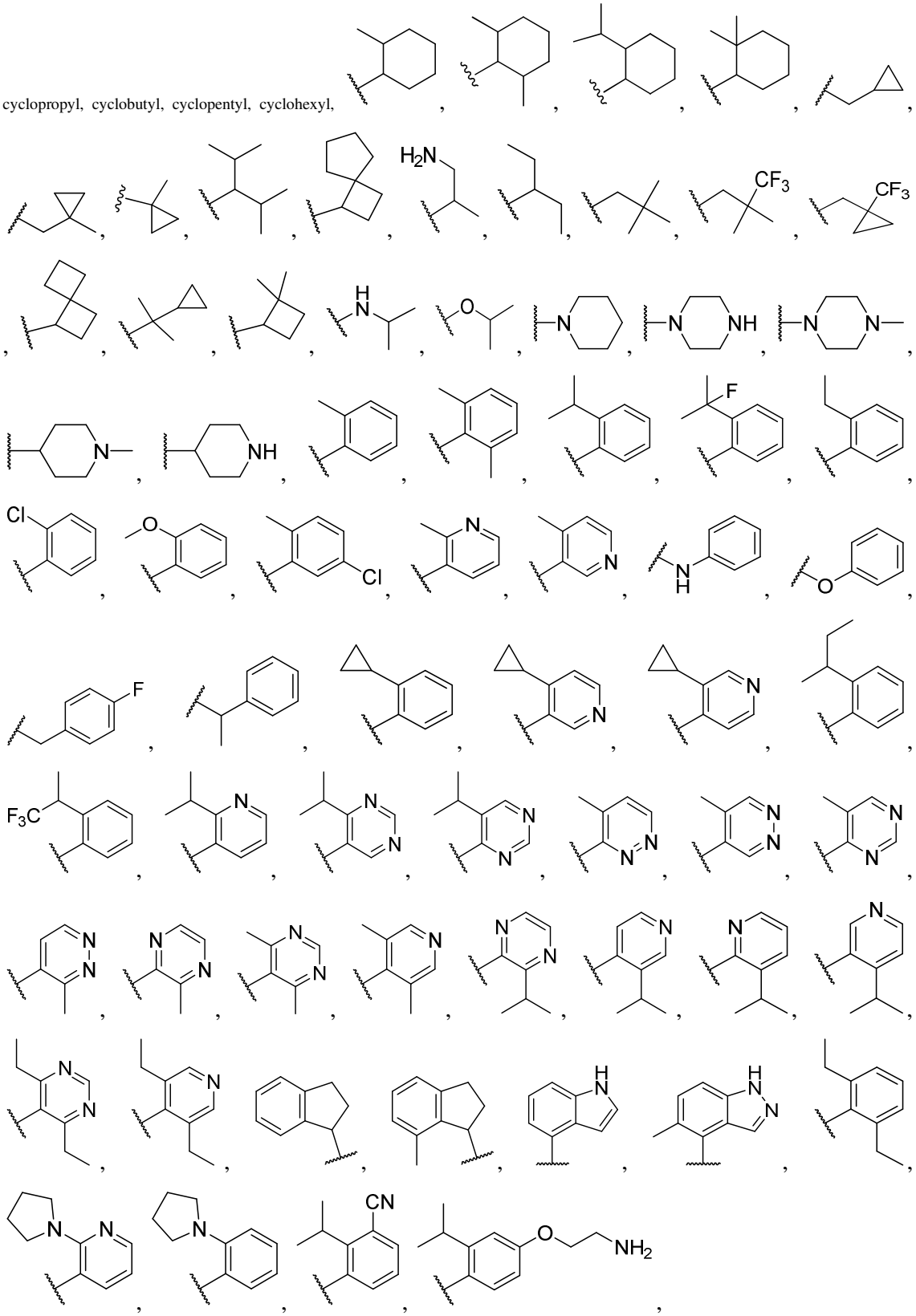
R^5 and R^6 are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6} alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{1-6}alkyleneamine, C_{0-6} alkylene-amide, C_{0-3}alkylene-C(O)OH, C_{0-3}alkylene-C(O)OC_{1-4}alkyl, C_{1-6} alkylene-O-aryl, C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, 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;

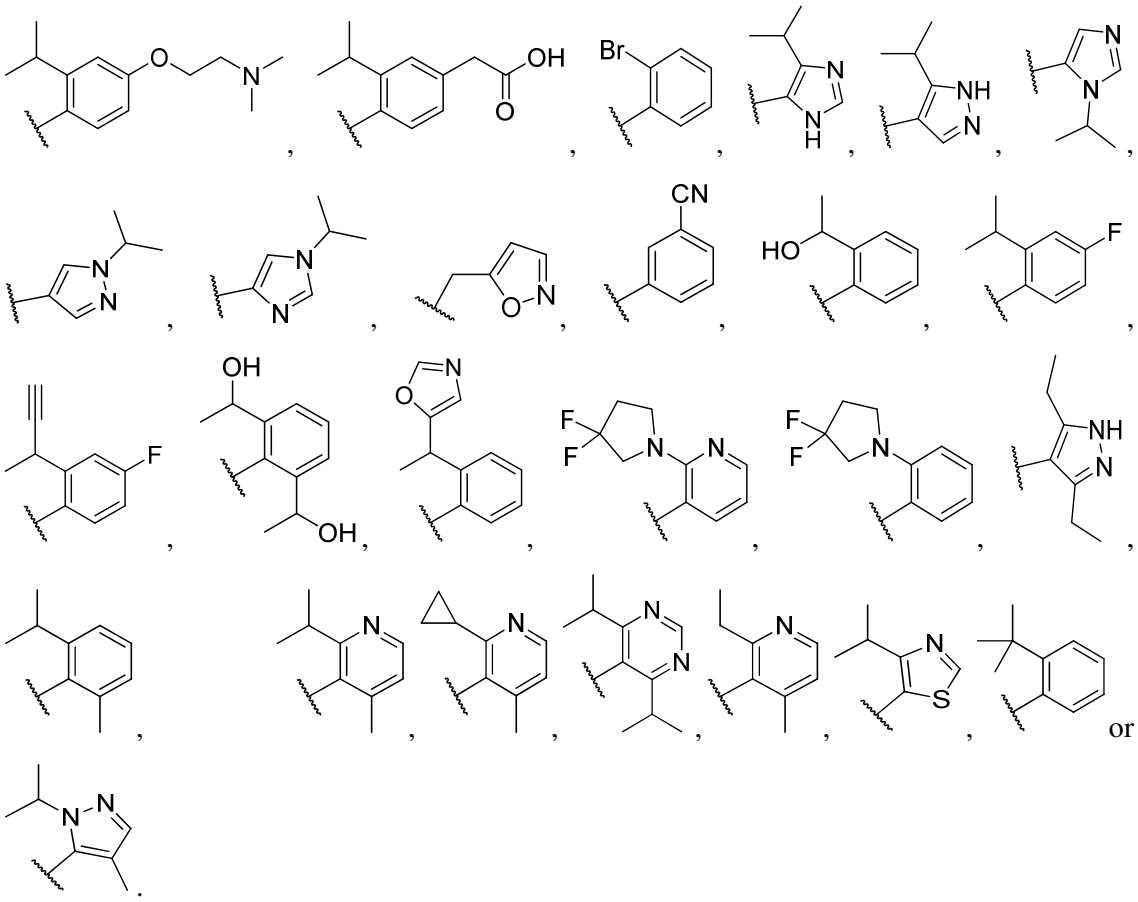
R^7 is H or C_{1-8}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring; and

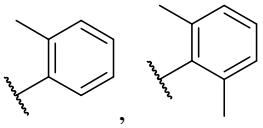
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{3-14}heteroaryl, C_{0-3} alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-C_{3-14}heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3}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

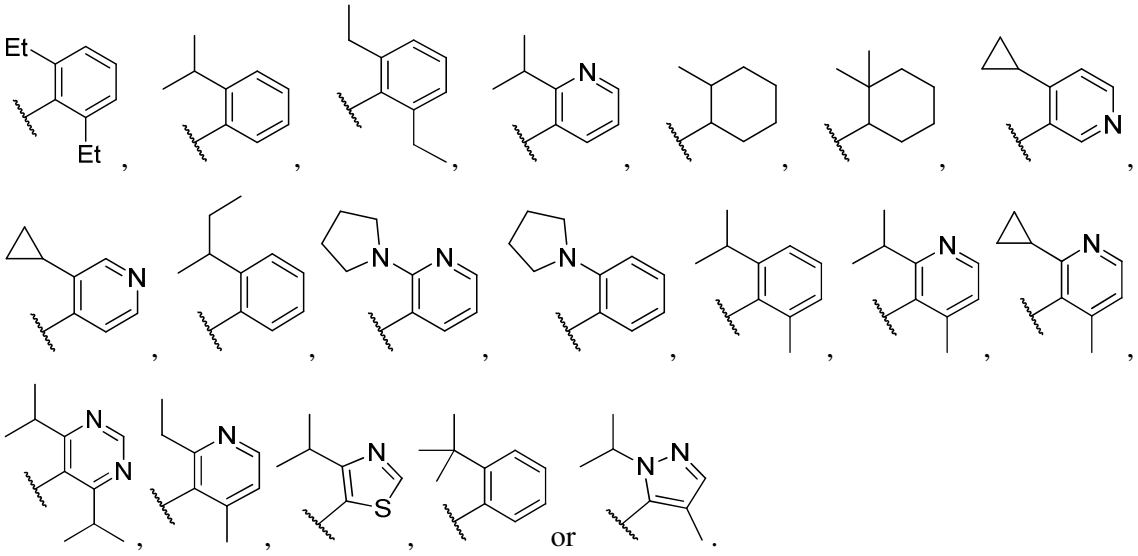
[0020] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some example, each of E^1 and E^2 is CR^1. In other example, E^1 is CR^1 and E^2 is N. In some example, E^1 is N and E^2 is CR^1. In various example, each 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 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 example, R^{10} is C_{1-8}alkyl. In some example, R^{10} is C_{0-3}alkylene-C_{6-14}aryl. In some example, R^{10} is C_{0-3} alkylene-C_{2-14}heteroaryl. In some example, R^{10} is C_{0-3}alkylene-C_{3-14} cycloalkyl. In some example, R^{10} is C_0

$_{-3}$alkylene-C_{2-14}heterocycloalkyl. In other 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, 

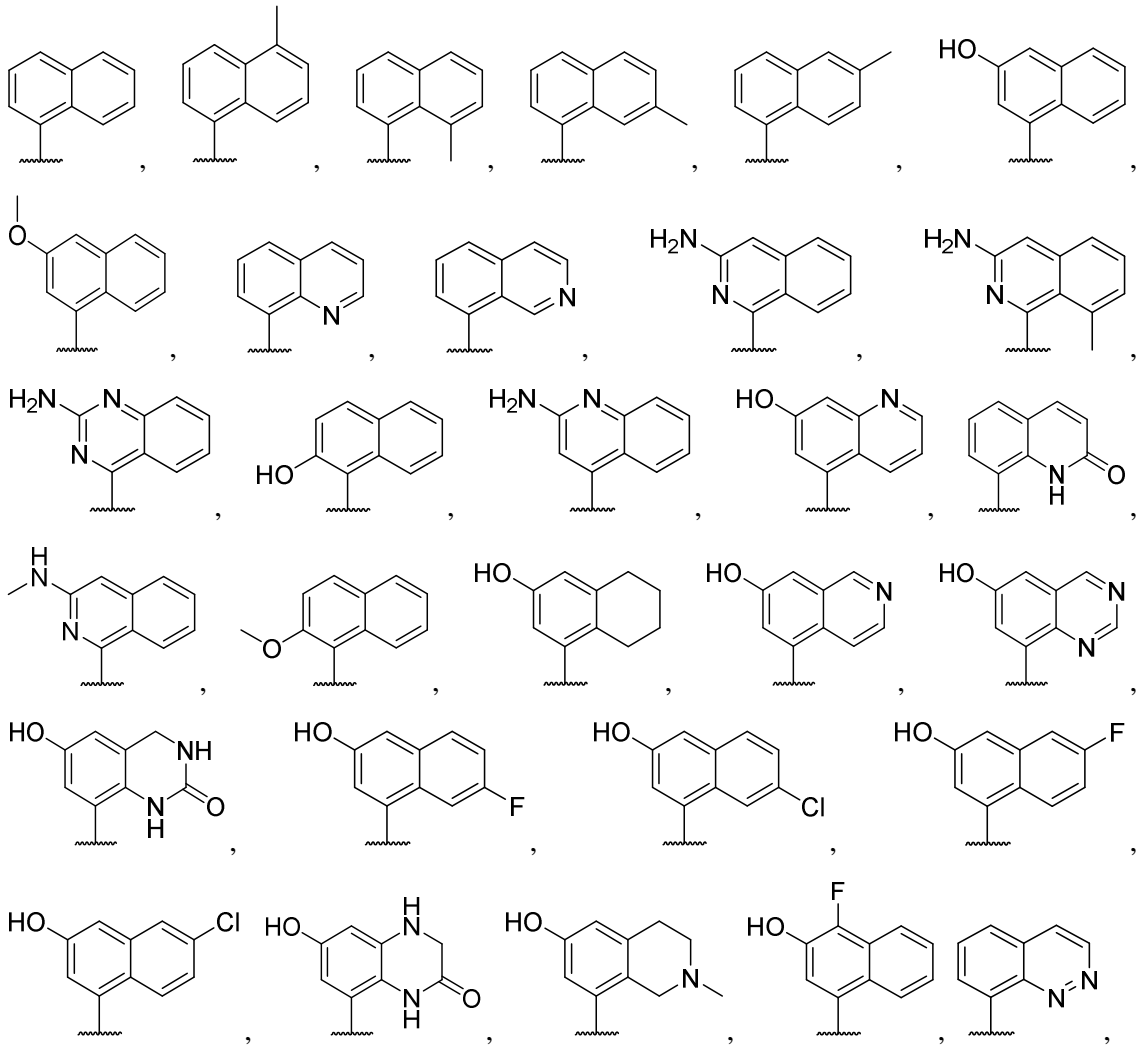


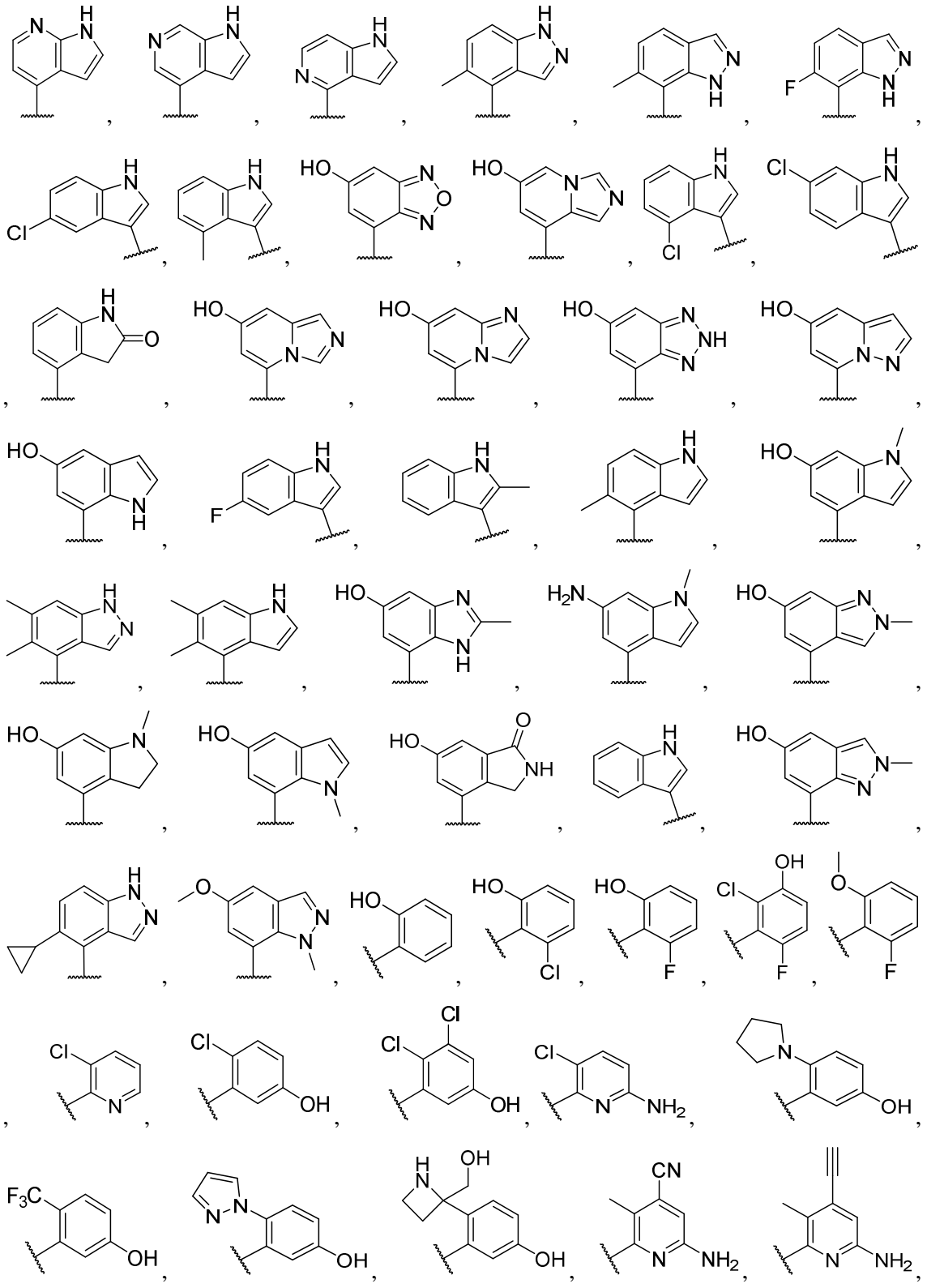
[0022] In some example, R^{10} comprises an ortho-substituted aryl, ortho-substituted heteroaryl, or 2-substituted cyclohexyl. For example, R^{10} can be 

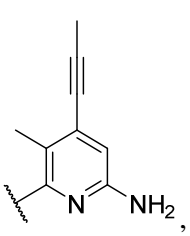
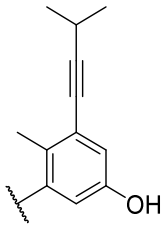
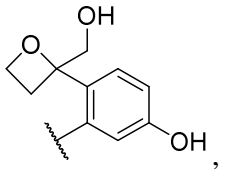
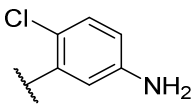
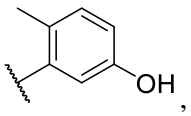
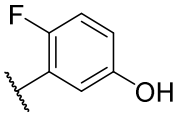
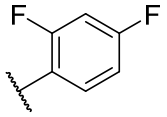


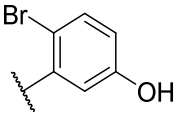
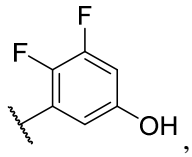
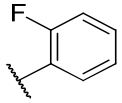
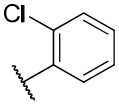
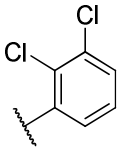
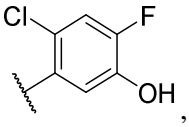
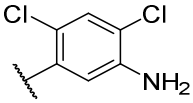
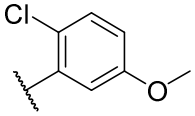
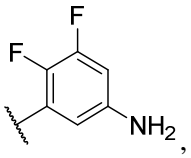
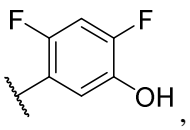
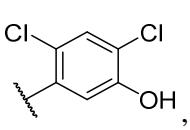
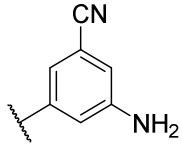
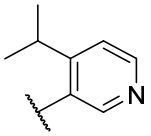
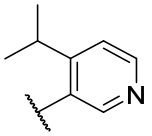
[0023] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some example, R^1 is H. In some example, R^1 is F. In some example, R^1 is methyl.

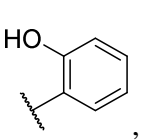
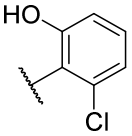
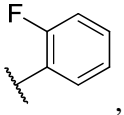
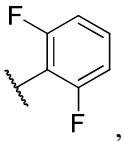
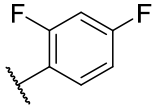
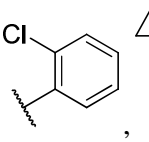
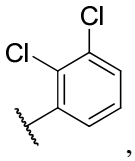
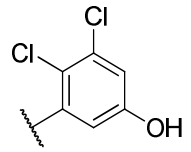
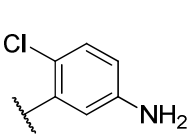
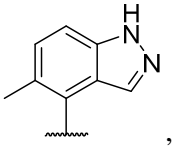
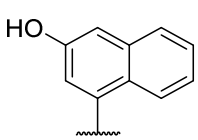
[0024] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various example, R^2 is aryl. In some example, R^2 is heteroaryl. In various example, R^2 is phenyl, naphthyl, pyridyl, indazolyl, indolyl, azaindolyl, 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,





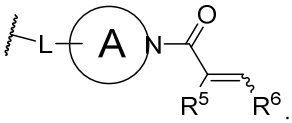
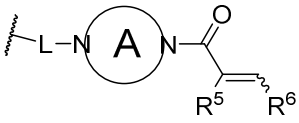
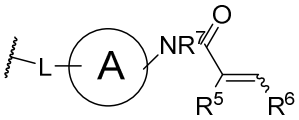
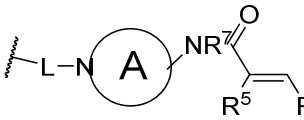
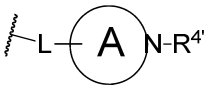
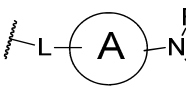
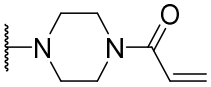
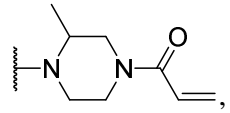
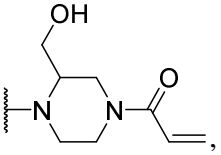
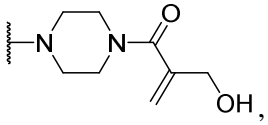
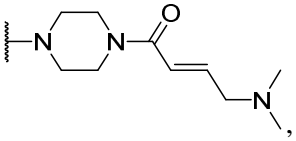
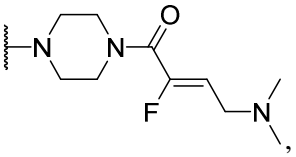
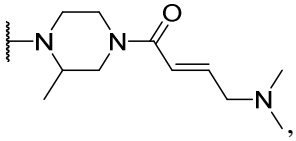
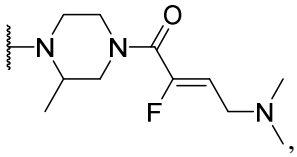
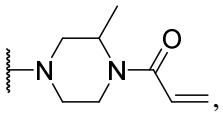
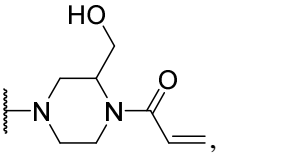
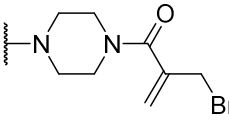
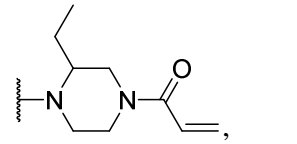
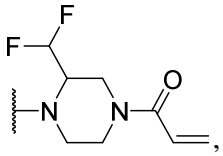
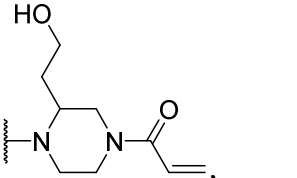
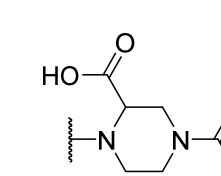
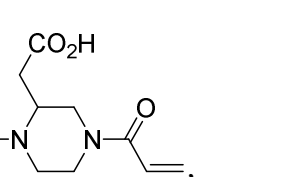
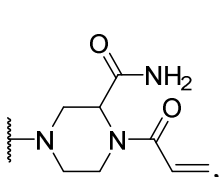
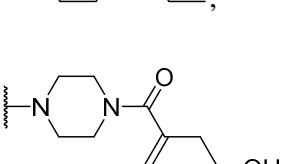
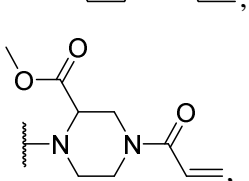
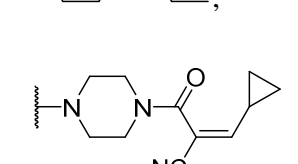
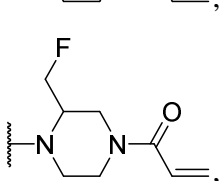
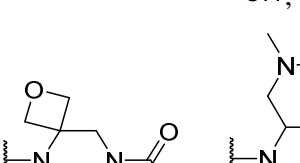
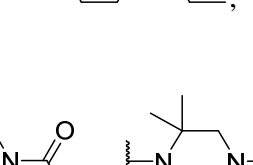
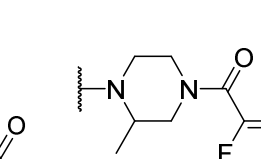
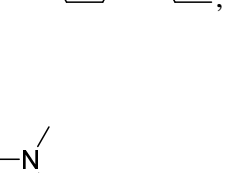
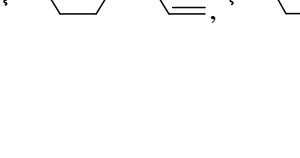
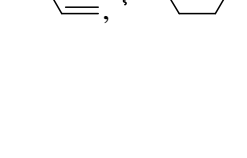
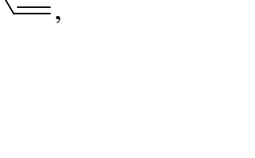








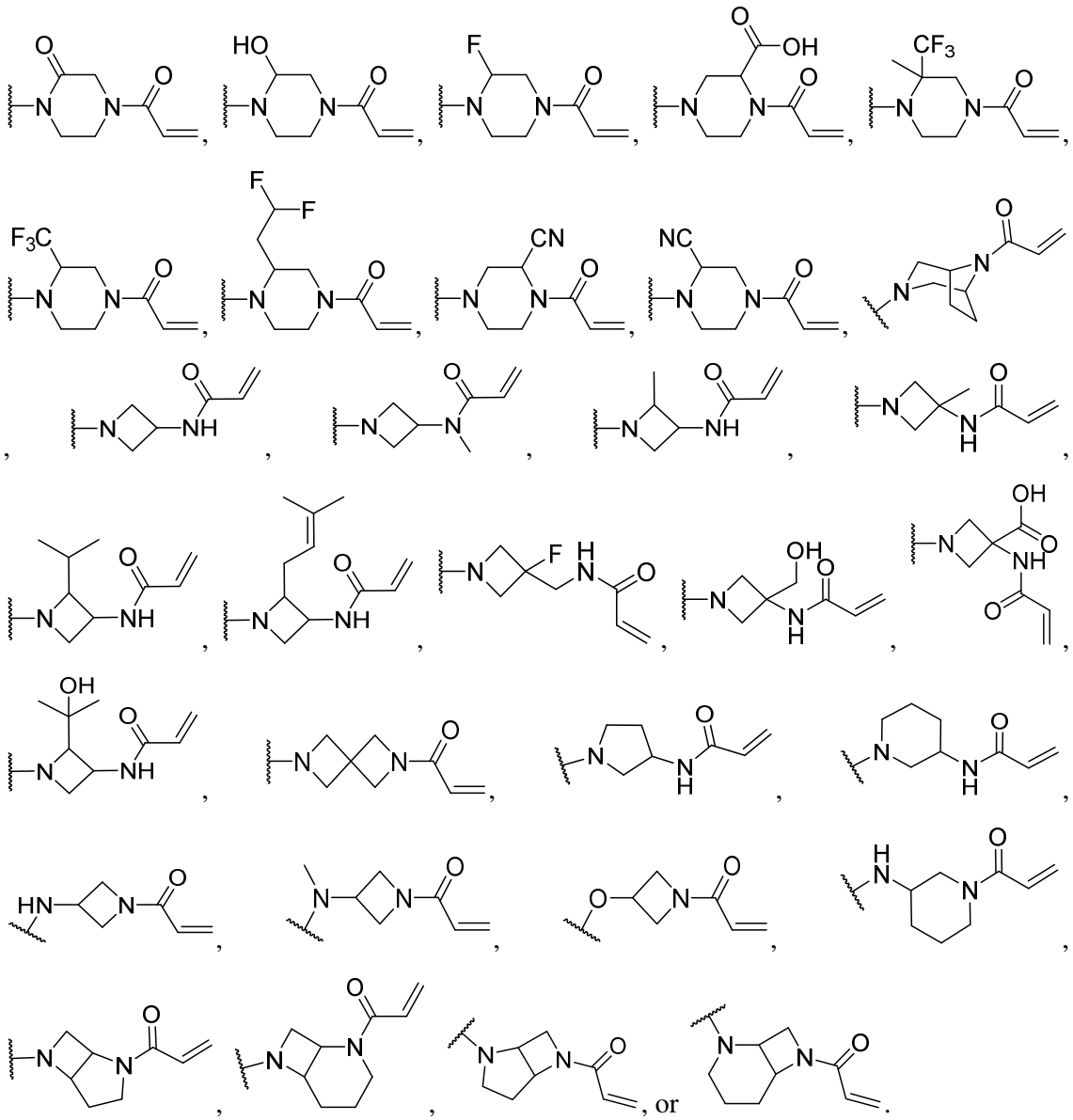













, or .

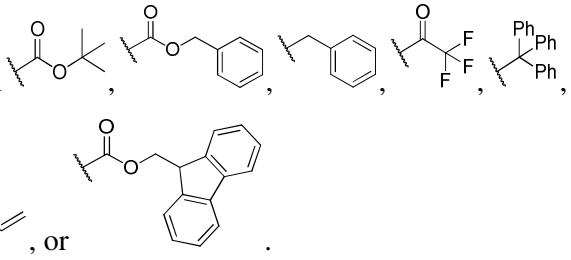
[0025] In various example, R^2 can be bromine, , , , , , , , , , , , , and .

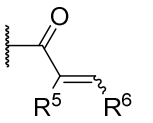
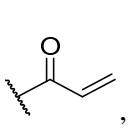
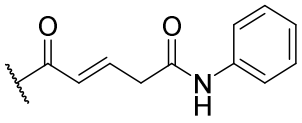
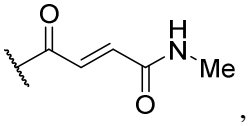
[0026] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various example, R^3 is halo. In various example, R^3 is Cl. In various example, R^3 is F. In some example, R^3 is C_{1-2}alkyl. In some example, R^3 is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

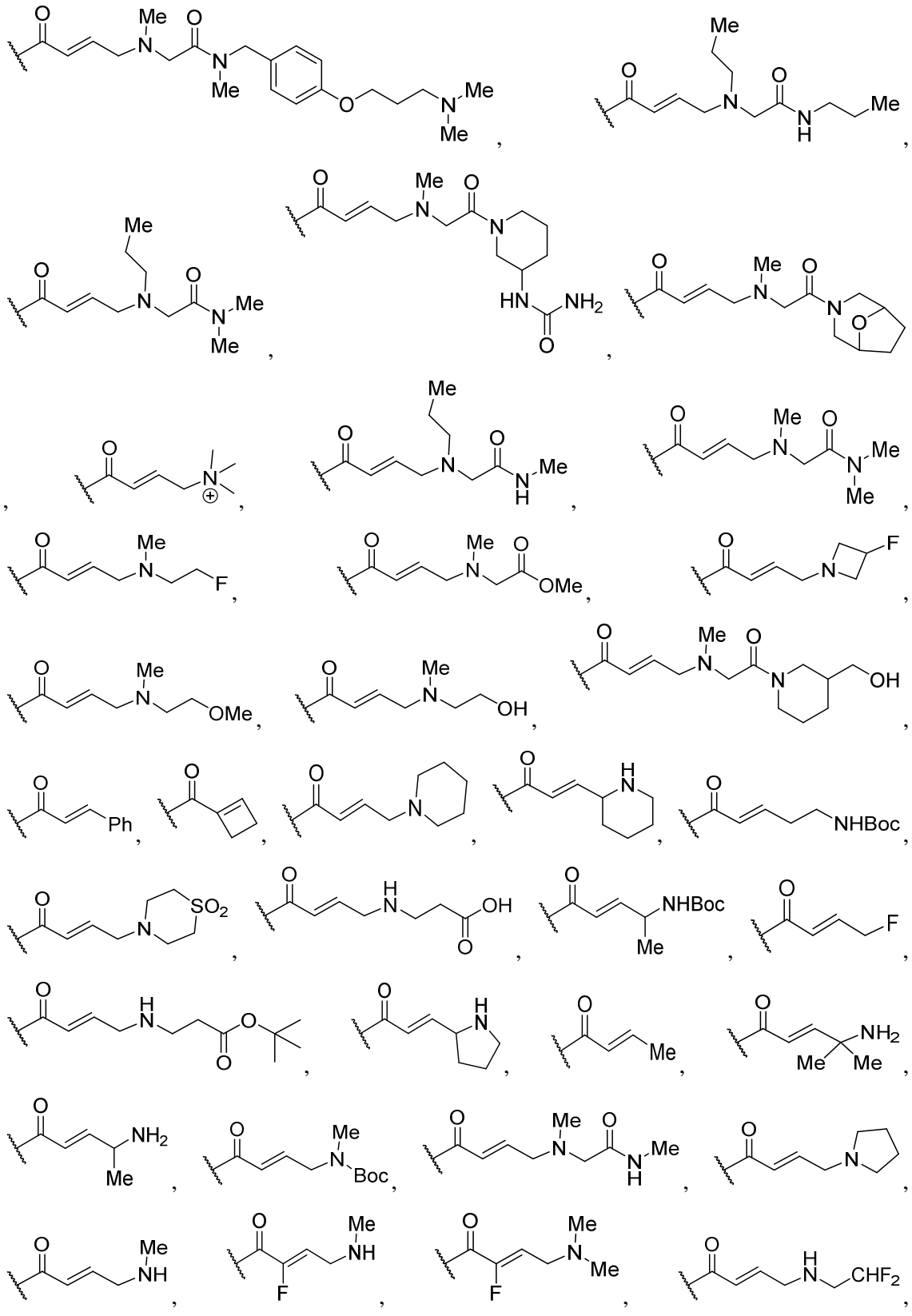
[0027] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some example, R^4 is

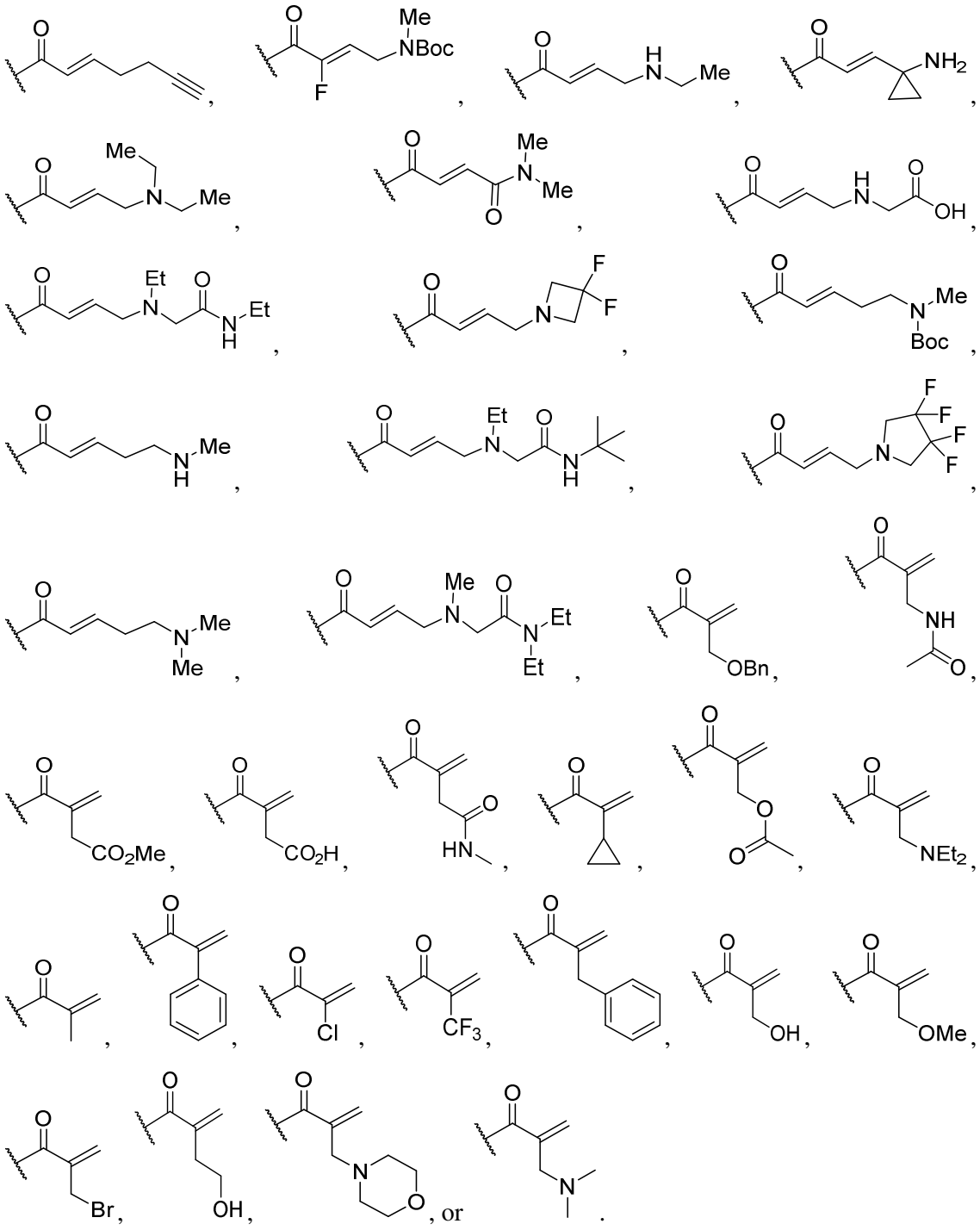

. In various example, R^4 is 
. In some example, R^4 is 
. In some example, R^4 is 
. In some example, R^4 is 
. In some example, R^4 is 
. In some example, R^4 can be 
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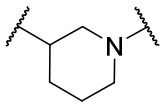
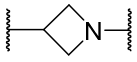


[0028] In various example $R^{4'}$ is H, C_{1-8}alkyl, C_{2-8}alkynyl, C_{1-6}alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{0-3}alkylene-C_{3-8}cycloalkyl, C_{0-3}alkylene-C_{2-7}heterocycloalkyl, C_{0-3}alkylene-C_{6-14}aryl, or selected from 

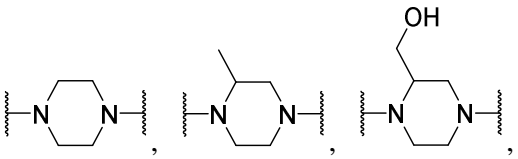
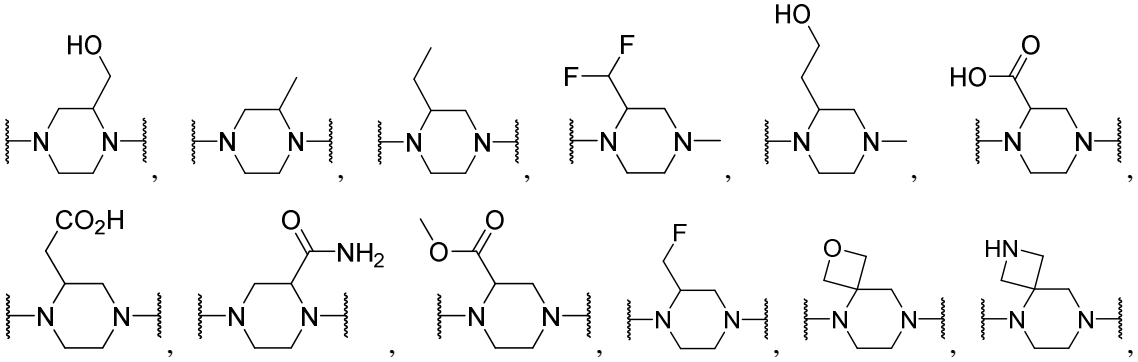
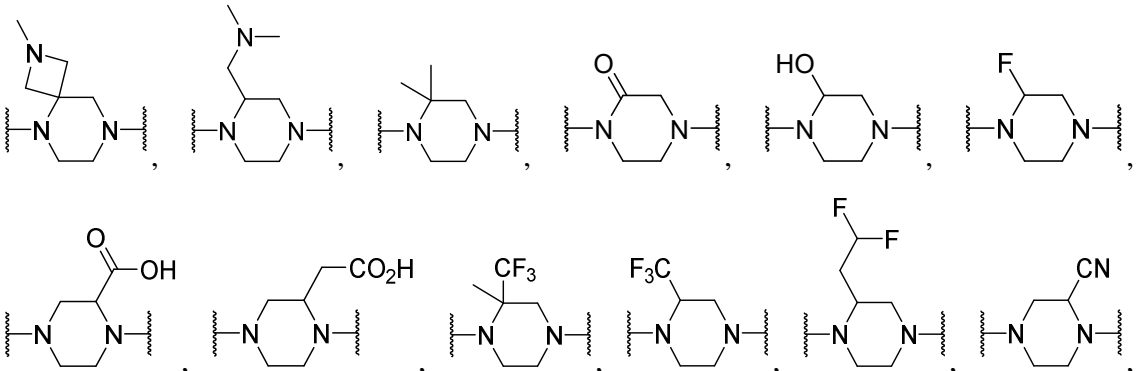
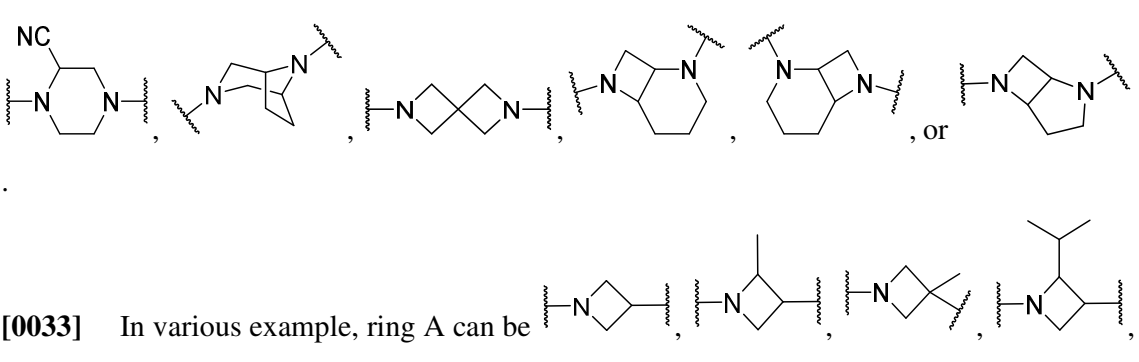
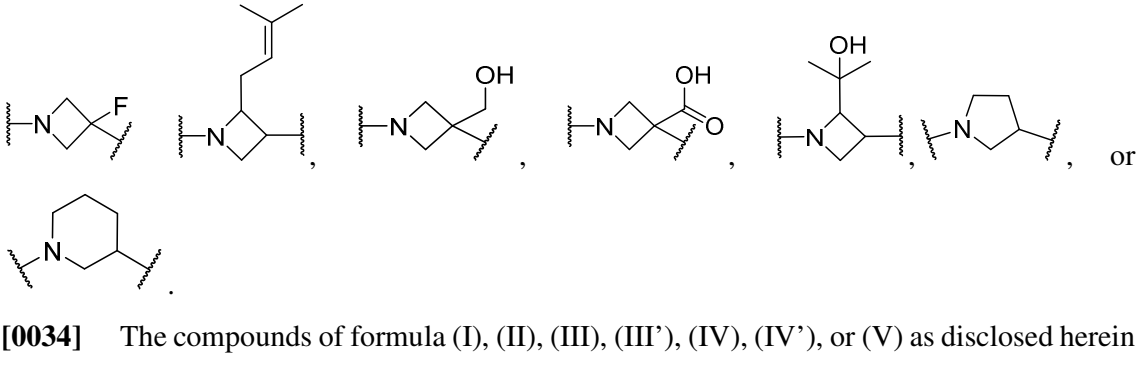
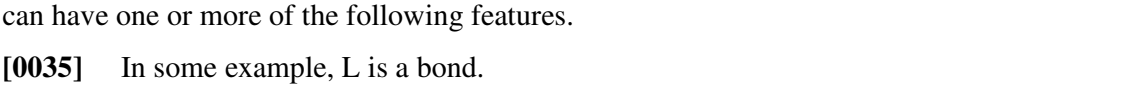
[0029] In various example,  can be , , ,





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

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

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

[0033] In various 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.

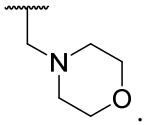
[0035] In some example, L is a bond.

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

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

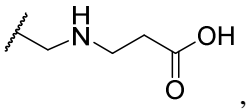
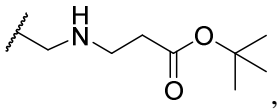
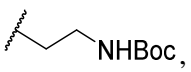
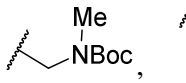
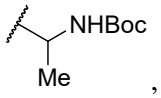
[0038] In various example, L is NH.

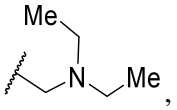
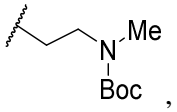
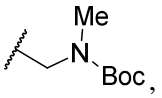
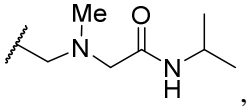
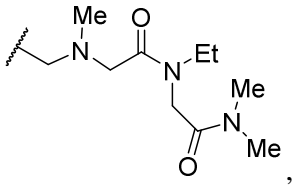
[0039] In some example, R^5 is H or halo.

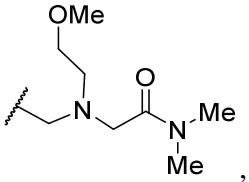
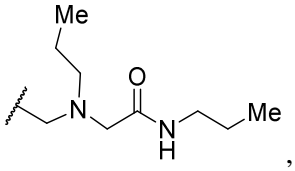
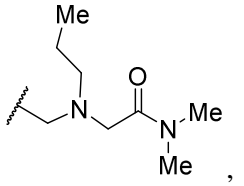
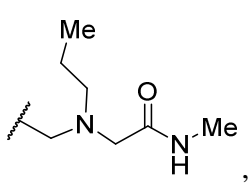
[0040] In some example, R^5 is H, Br, Cl, F, CN, CH_3, CF_3, CH_2Br, CH_2OH, CH_2CH_2OH, CH_2OCH_2phenyl, cyclopropyl, phenyl, CH_2phenyl, CH_2OCH_3, $CH_2N(CH_3)_2$, $CH_2N(CH_2CH_3)_2$, CH_2CO_2H, $CH_2CO_2CH_3$, $CH_2NHC(O)CH_3$, $CH_2C(O)NHCH_3$, $CH_2OC(O)CH_3$, or .

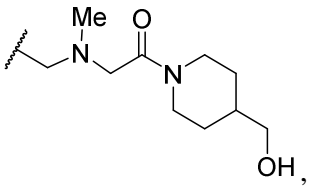
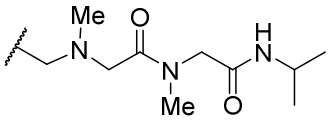
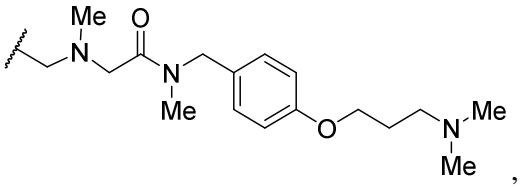
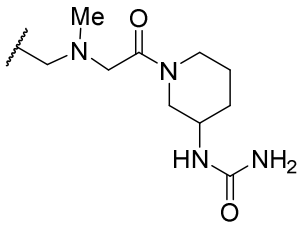
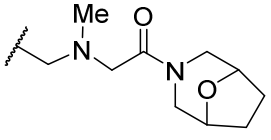
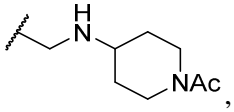
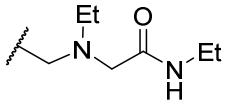
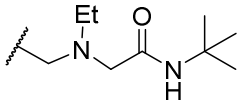
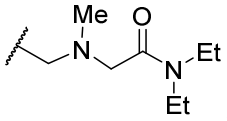
[0041] In some example, R^6 is C_{1-6}alkyl, C_{1-6}alkylene-O-$C_{1\text{-}6}$alkyl, C_{1-6}alkylene-OH, C_{1-3}haloalkyl, C_{1-6}alkylene-amine, C_{0-6}alkylene-amide, C_{0-1}alkylene C(O)O$C_{1\text{-}3}$alkyl, C_{0-1}alkylene-$C_{2\text{-}14}$heterocycloalkyl, C_{0-1}alkylene-$C_{3\text{-}14}$cycloalkyl,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

[0042] In various example, R^6 is C_{0-6}alkylene-amine or C_{0-3}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, $CH_2NH(CH_3)CH_2CH_2OH$, $CH_2NH(CH_3)CH_2CH_2F$, $CH_2N^+(CH_3)_3$, $CH_2NHCH_2CHF_2$, $CH_2NHCH_2CH_3$,

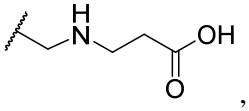
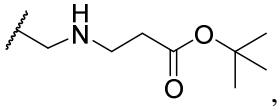
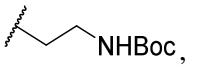
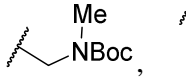
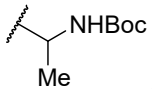
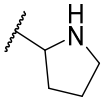
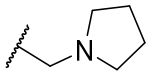
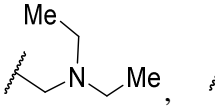
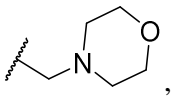
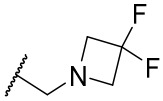
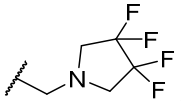
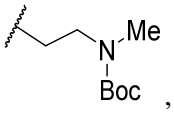
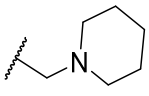
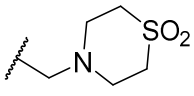
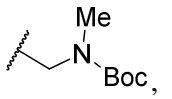
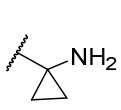
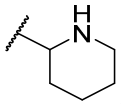
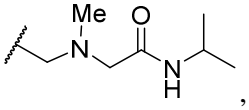
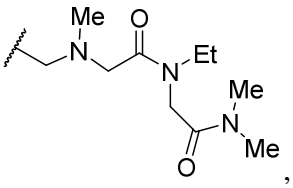
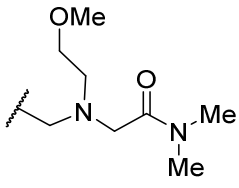
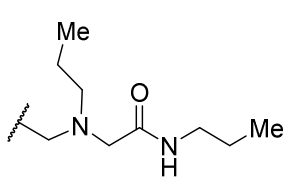
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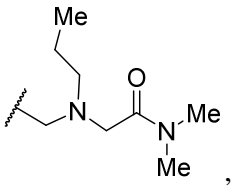
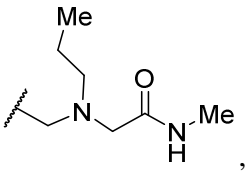
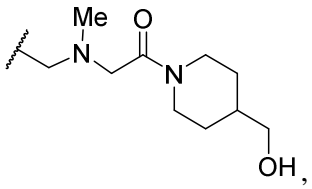
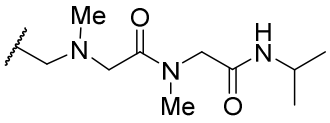
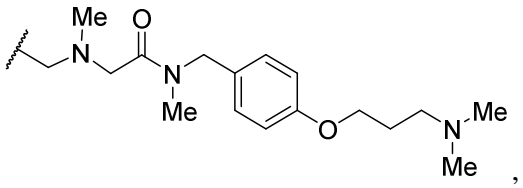
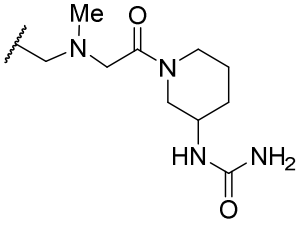
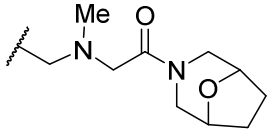
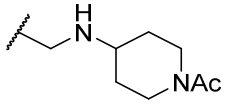
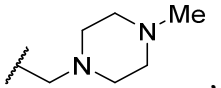
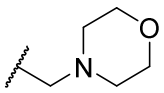
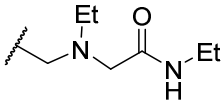
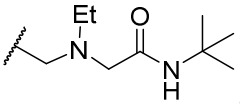
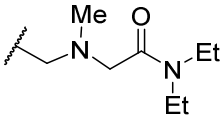
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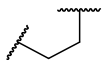
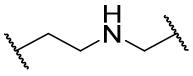
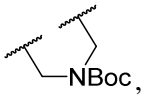
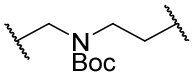
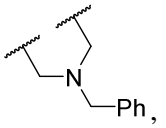
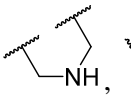
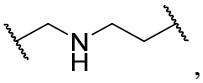
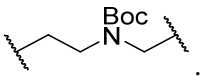

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[0043] In various example, R^6 is phenyl, cyclopropyl, CH_3, CF_3, CH_2CH_3, CH_2NH_2, $CH(CH_3)NH_2$, $CH(CH_3)_2NH_2$, CH_2Cl, CH_2Br, CH_2OCH_3, $CH_2Ophenyl$, CH_2OH, CO_2H, $CO_2CH_2CH_3$, CH_2CO_2H, $CH_2CH_2NH_2$, CH_2CH_2OH, $CH_2CH_2N(CH_3)_2$, CH_2NHCH_3, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $CH_2C(O)NHphenyl$, 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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[0044] In various example, R^5 and R^6 together are

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[0045] In some example, each of R^5 and R^6 is H.

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

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

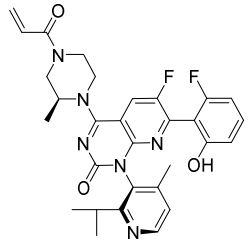
[0048] In various example, R^7 and R^5 together are $–CH_2–$ or $–C(O)CH_2–$.

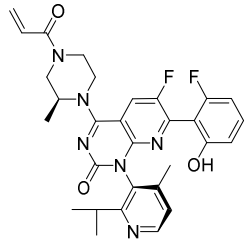
[0049] The compounds disclosed herein can be in the form of a pharmaceutically acceptable salt. The compounds provided can be formulated into a pharmaceutical formulation comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

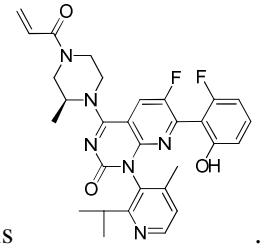
[0050] Also provided is a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with a compound or composition disclosed herein. Further provided is a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound or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

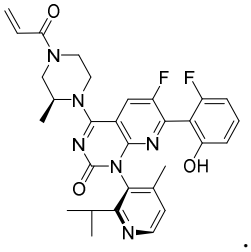
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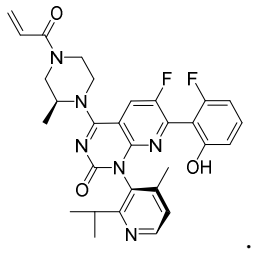
What is claimed is:

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.

3. A compound wherein the compound is  .

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).

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

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

10. Use of the compound of any one of Claims 1-7 in the manufacture of a medicament for treating cancer in a subject.

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.

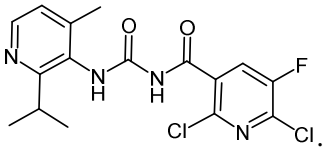
12. The use of claim 10, wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

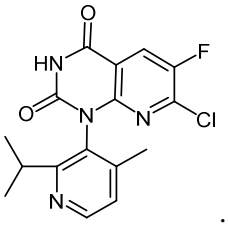
13. The use of claim 12, wherein cancer is non-small cell lung cancer.

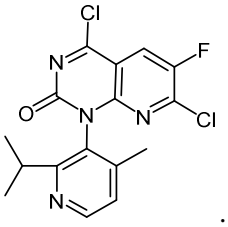
14. The compound for use according to claim 12, wherein the cancer is colorectal cancer.

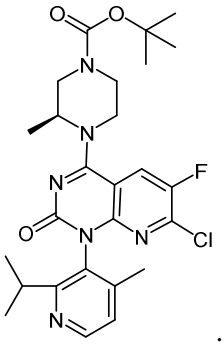
15. The compound for use according to claim 12, wherein the cancer is pancreatic cancer.

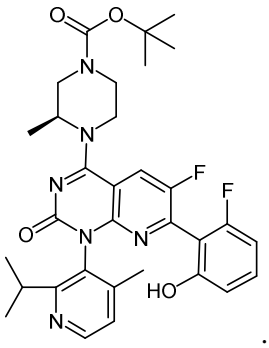
16. The compound for use according to any one of claims 12-15, wherein the cancer is mediated by a KRAS G12C mutation.

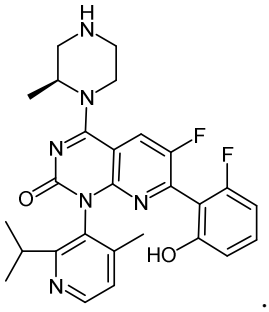
17. A compound, wherein the compound is .

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.