KRAS G12C INHIBITORS AND METHODS OF USING THE SAME

FIELD OF INVENTION

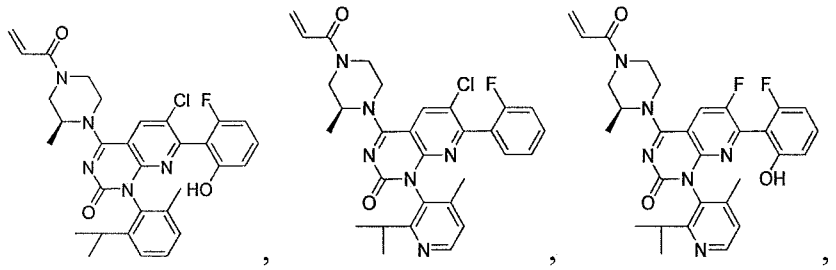
[0001] Provided herein are KRAS G12C inhibitors, composition of the same, and methods of using the same. These inhibitors are useful for treating a number of disorders, including pancreatic, colorectal, and lung cancers.

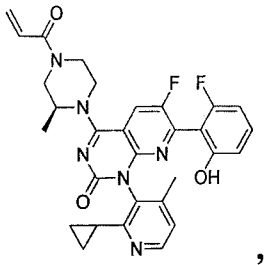
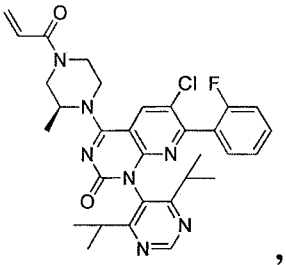
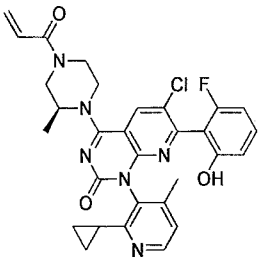
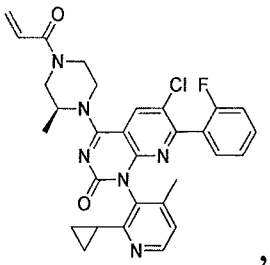
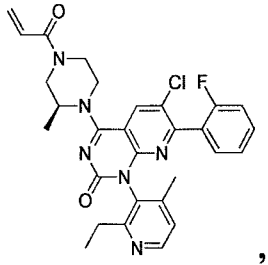
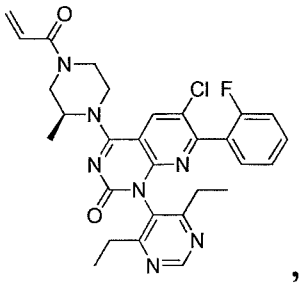
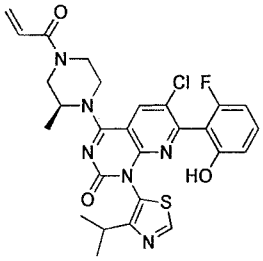
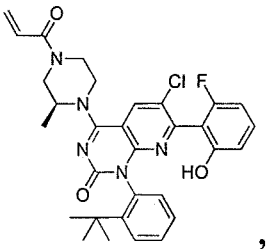
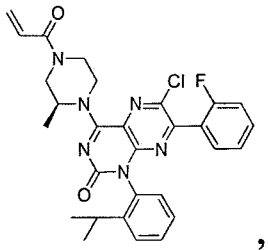
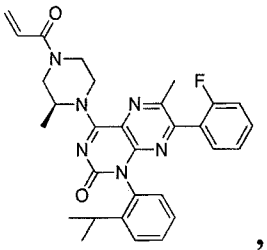
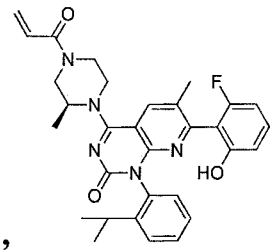
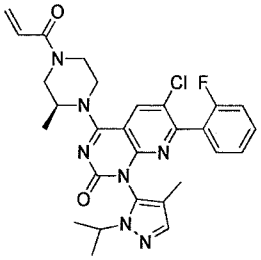
BACKGROUND

[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

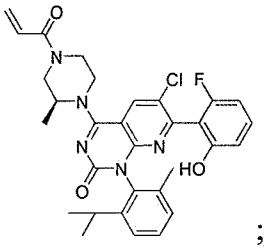
[0002a] In one aspect, the present disclosure refers to a compound having a structure selected from:




,

,

,

,

,

,

,

,

,

,

and

;

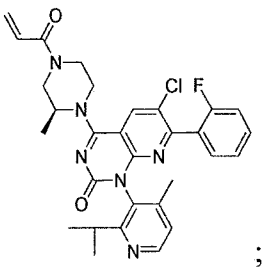
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0002b] In another aspect, the present disclosure refers to a compound having a structure


;

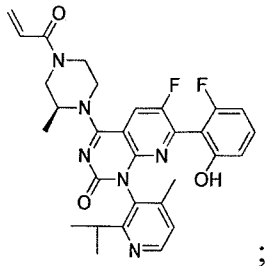
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0002c] In another aspect, the present disclosure refers to a compound having a structure


;

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

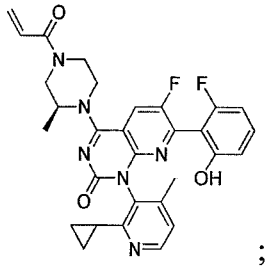
[0002d] In another aspect, the present disclosure refers to a compound having a structure



;

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

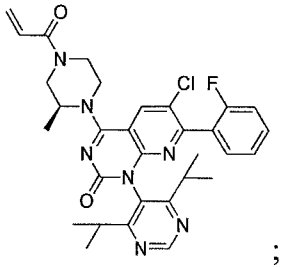
[0002e] In another aspect, the present disclosure refers to a compound having a structure



;

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

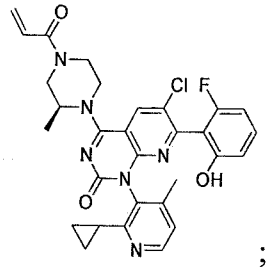
[0002f] In another aspect, the present disclosure refers to a compound having a structure



;

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

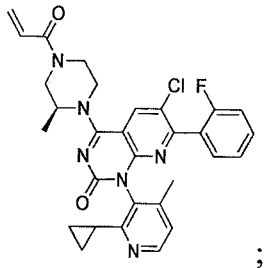
[0002g] In another aspect, the present disclosure refers to a compound having a structure



;

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

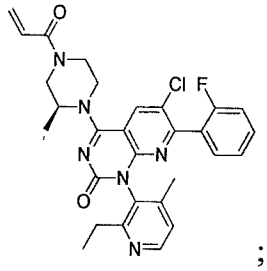
[0002h] In another aspect, the present disclosure refers to a compound having a structure



;

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

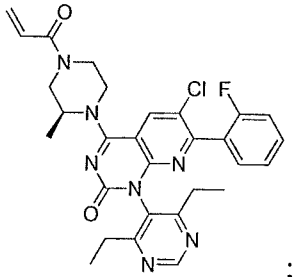
[0002i] In another aspect, the present disclosure refers to a compound having a structure



;

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

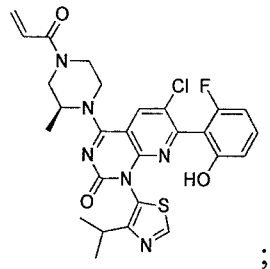
[0002j] In another aspect, the present disclosure refers to a compound having a structure



;

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

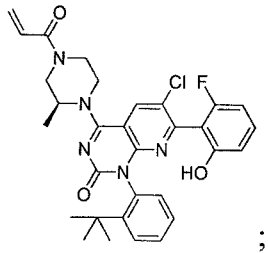
[0002k] In another aspect, the present disclosure refers to a compound having a structure



;

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

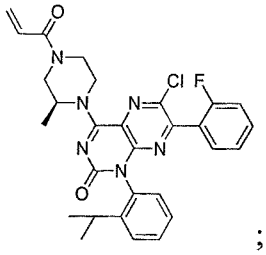
[0002l] In another aspect, the present disclosure refers to a compound having a structure



;

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

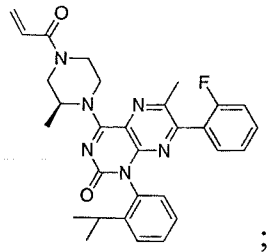
[0002m] In another aspect, the present disclosure refers to a compound having a structure



;

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

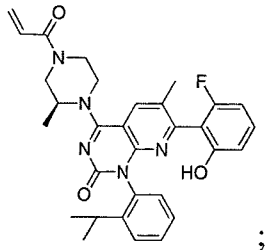
[0002n] In another aspect, the present disclosure refers to a compound having a structure



;

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

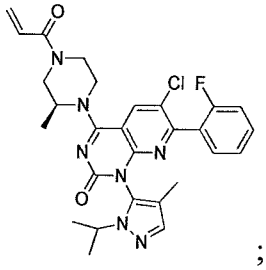
[0002o] In another aspect, the present disclosure refers to a compound having a structure



;

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

[0002p] In another aspect, the present disclosure refers to a compound having a structure



;

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

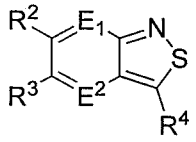
[0002q] In another aspect, the present disclosure refers to a pharmaceutical formulation comprising any one or more of the compounds of claims as described herein and a pharmaceutically acceptable excipient.

[0002r] In another aspect, the present disclosure refers to an *in vitro* method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound as described herein or the composition as described herein.

[0002s] In another aspect, the present disclosure refers to the use of the compound as described herein or the composition as described herein in the manufacture of a medicament for treating cancer in a subject.

[0002t] In another aspect, the present disclosure refers to a compound as described herein for use in treating cancer.

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



(I)

wherein

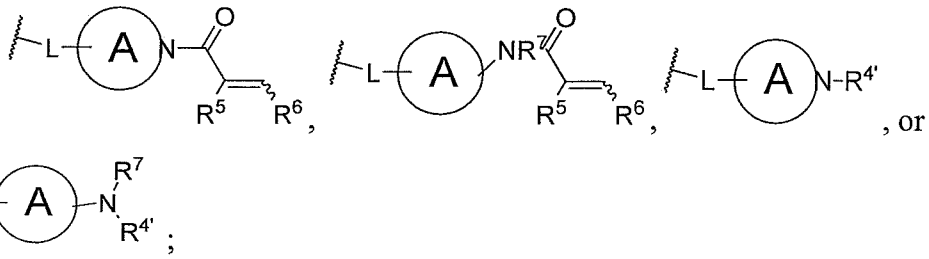
E^1 and E^2 are each independently N or CR^1;

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



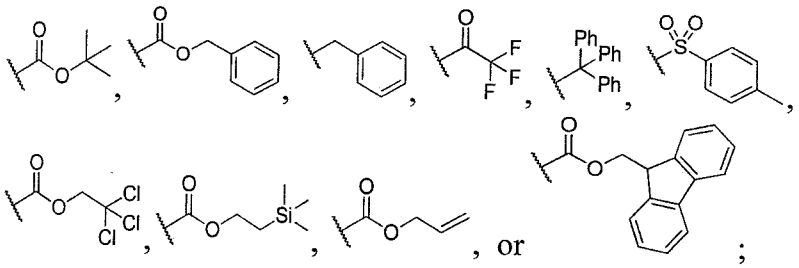
;

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



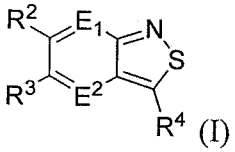
; and

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

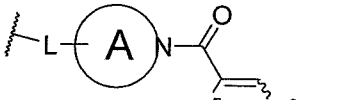
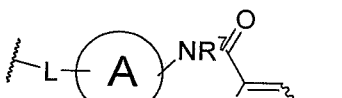
E^1 and E^2 are each independently N or CR^1;

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;

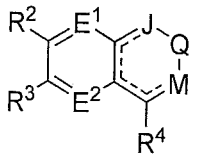
L is a bond, C_{1-6}alkylene, -O-C_{0-5}alkylene, -S-C_{0-5}alkylene, or -NH-C_{0-5} alkylene, and for C_{2-6}alkylene, -O-C_{2-5}alkylene, -S-C_{2-5}alkylene, and NH-C_{2-5} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

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,

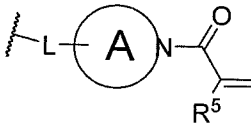
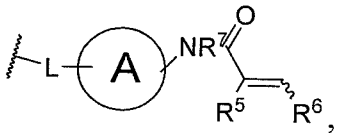
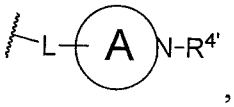
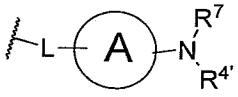
or a pharmaceutically acceptable salt thereof.

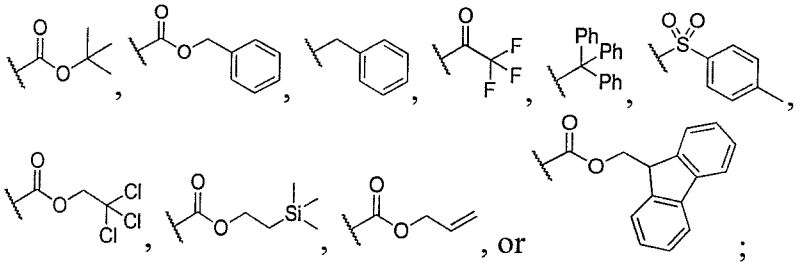
[0005] Further provided are compounds of formula (II), or a pharmaceutically acceptable salt thereof:



(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};

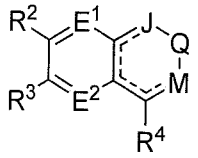
(2) when M is NR^{13}, J is N or CR^{10};

(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};

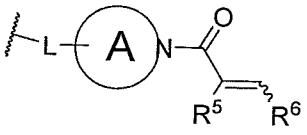
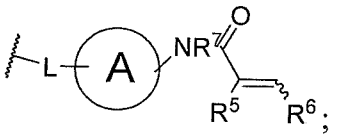
M is N, NR^{13}, or CR^{13};

=== 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};

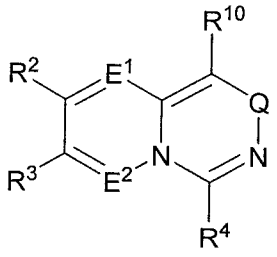
(2) when M is NR^{13}, J is N or CR^{10};

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

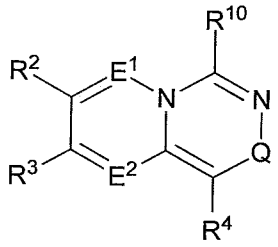
(4) when M is CR^{13}, J is N or NR^{10}.

[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



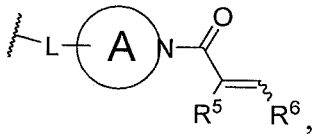
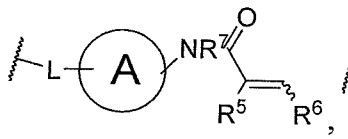
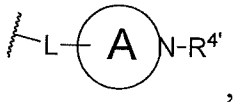
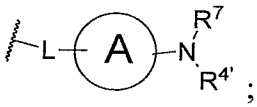
(III'),

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;

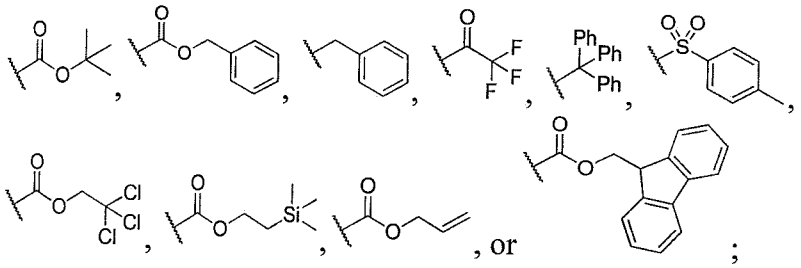
R^3 is halo, C_{1-3}alkyl, C_{1-2}haloalkyl, C_{1-3}alkoxy, C_{3-4}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3} alkenyl, C_{2-3}alkynyl, aryl, or heteroaryl;

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_{1-6}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;

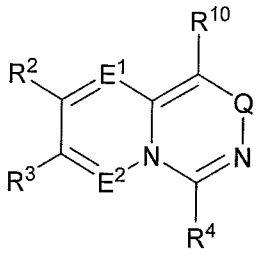
R^7 is H or C_{1-8}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

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

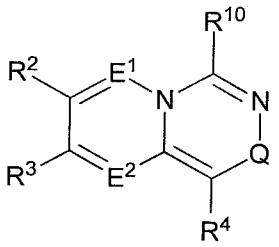
R^8 and R^9 are each independently H, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, cyano, nitro, or C_{3-14}cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

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.

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



(III) or



(III')

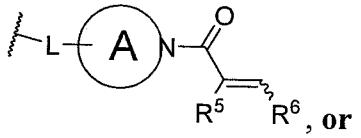
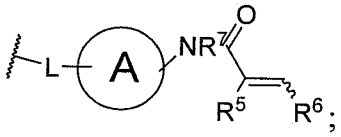
wherein

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 $C=NR^8$;

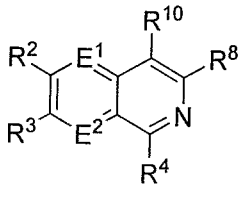
R^8 and R^9 are each independently H, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, cyano, nitro, or C_{3-14}cycloalkyl, or R^8 and R^9, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

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.

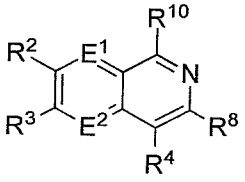
[0011] In some examples, the compouds have a structure of formula (III). In other examples, the compouds have a structure of formula (III').

[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



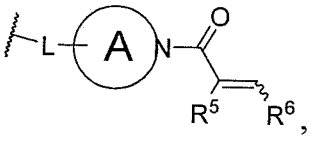
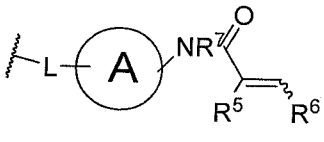
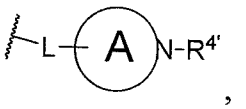
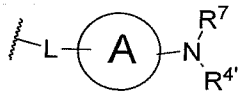
(IV') E^1 and E^2 are each independently CR^1 or N;

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_{1-6}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_{3-4}cycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl,

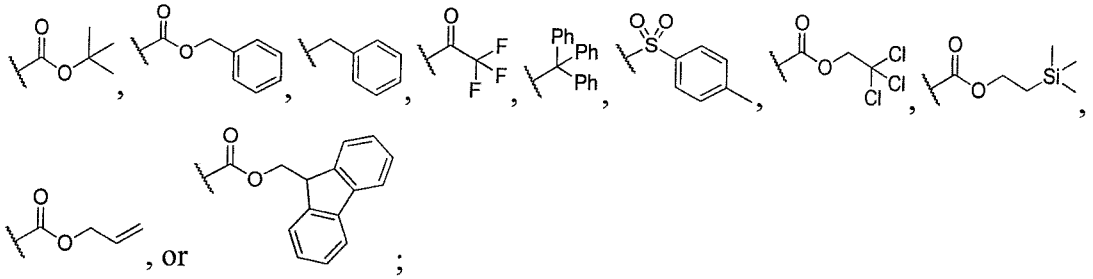
or heteroaryl;

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_{1-8}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;

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

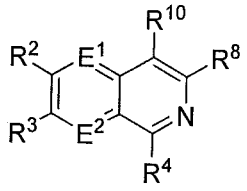
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{2-14}heteroaryl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-3}alkylene-C_{6-14}aryl, O-C_{0-}

$_3$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;

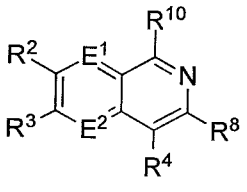
[0014] In some examples, the compouds disclosed herein have a structure of formula (IV). In various examples, the compouds disclosed herein have a structure of formula (IV'). In some examples, E^1 and E^2 are each CR^1, and R^8 is hydroxy, halo, nitro, or C_{3-6}cycloalkyl.

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

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



(IV) or



(IV')

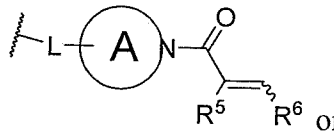
wherein

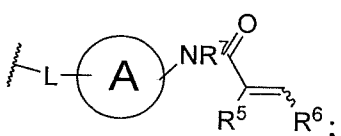
E^1 and E^2 are each independently CR^1 or N;

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

R^5 and R^6 are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6} alkylene-O-C_{1-}

$_4$alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{1-6}alkyleneamine, C_{0-6} alkylene-amide, C_{0-3}alkylene-C(O)OH, C_{0-3}alkylene-C(O)OC_{1-4}alkyl, C_{1-6} alkylene-O-aryl, C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{2-14}heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

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

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

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

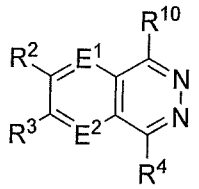
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{3-14}heteroaryl, C_{0-3} alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-C_{3-14}heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3}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

or a pharmaceutically acceptable salt thereof.

[0016] In some 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.

[0017] In some examples, R^8 is methyl.

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



(V)

wherein

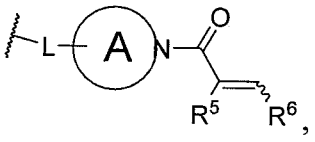
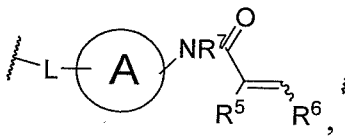
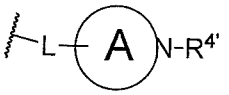
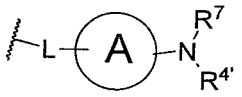
E^1 and E^2 are each independently CR^1 or N;

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-}

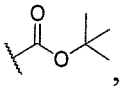
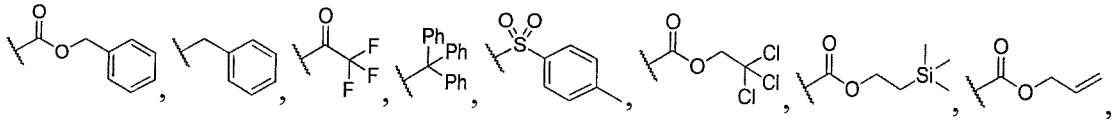
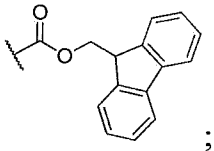
$_{3}$alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or C_{0-3}alkylene-C_{2-14}heteroaryl, and each R' is independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-14}cycloalkyl, C_{2-14}heterocycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, 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;

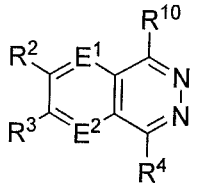
$R^{4'}$ is H, C_{1-8}alkyl, C_{2-8}alkynyl, C_{1-6}alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6} haloalkyl, cycloalklyl, heterocycloalkyl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or selected from , , or ;

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)

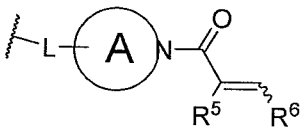
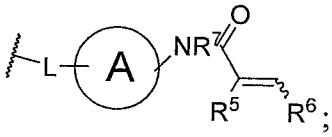
wherein

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-}

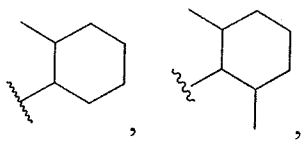
$_4$alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{1-6}alkyleneamine, C_{0-6} alkylene-amide, C_{0-3}alkylene-C(O)OH, C_{0-3}alkylene-C(O)OC_{1-4}alkyl, C_{1-6} alkylene-O-aryl, C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{3-14}cycloalkyl, 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;

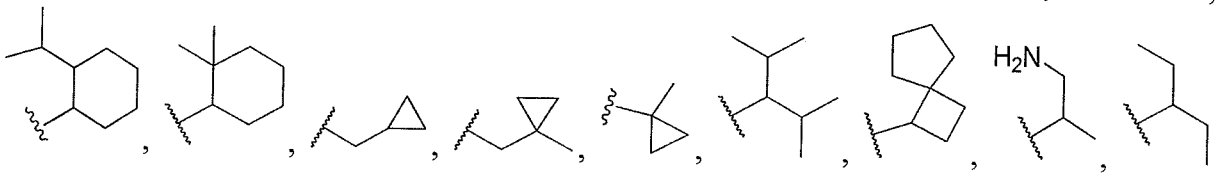
R^7 is H or C_{1-8}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring; and

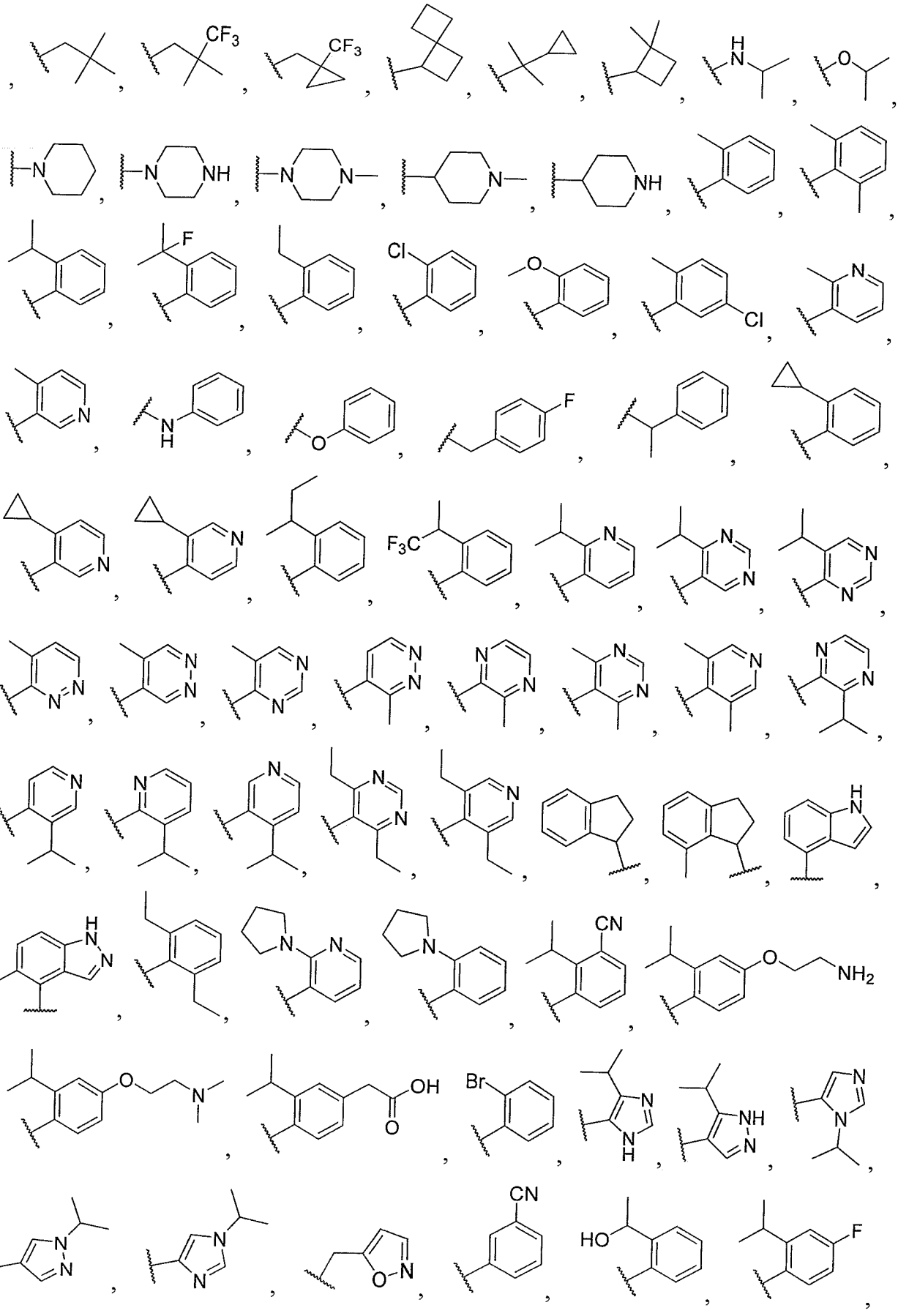
R^{10} is C_{1-8}alkyl, C_{0-3}alkylene-C_{6-14}aryl, C_{0-3}alkylene-C_{3-14}heteroaryl, C_{0-3} alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14}heterocycloalkyl, C_{1-6}alkoxy, O-C_{0-3} alkylene-C_{6-14}aryl, O-C_{0-3}alkylene-C_{3-14}heteroaryl, O-C_{0-3} alkylene-C_{3-14}cycloalkyl, O-C_{0-3}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

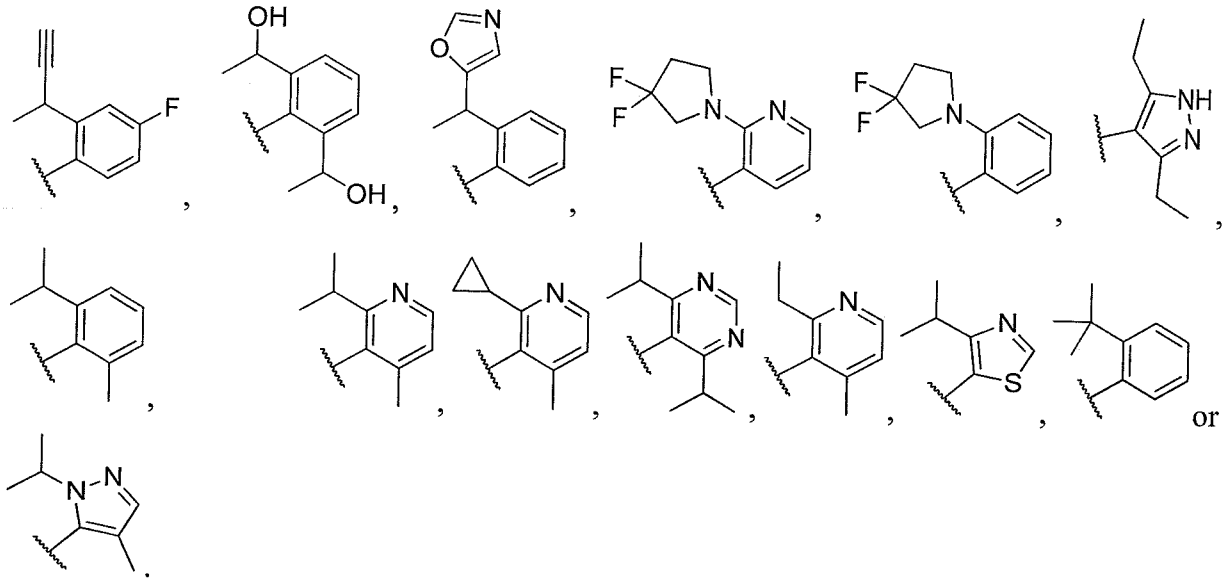
[0020] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some examples, each of E^1 and E^2 is CR^1. In other examples, E^1 is CR^1 and E^2 is N. In some examples, E^1 is N and E^2 is CR^1. In various examples,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

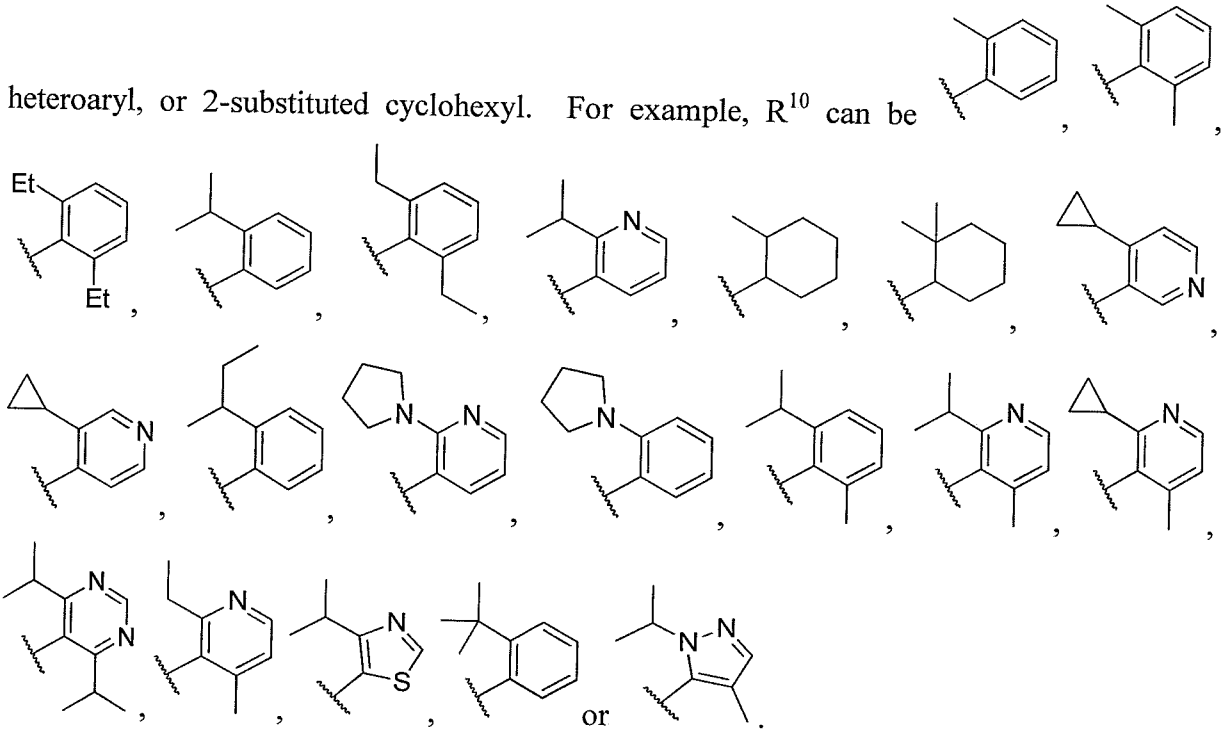








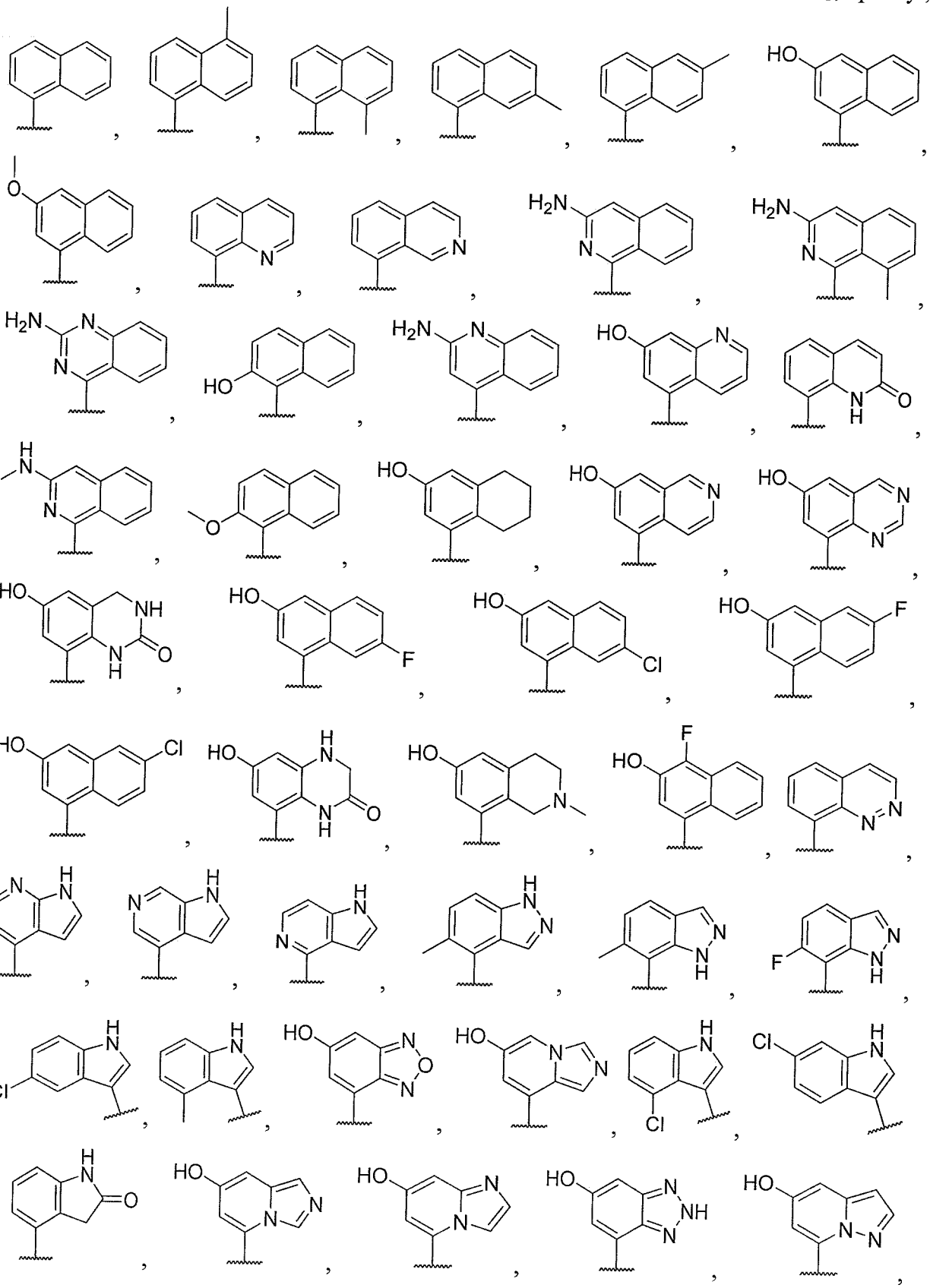
[0022] In some examples, R^{10} comprises an ortho-substituted aryl, ortho-substituted heteroaryl, or 2-substituted cyclohexyl. For example, R^{10} can be

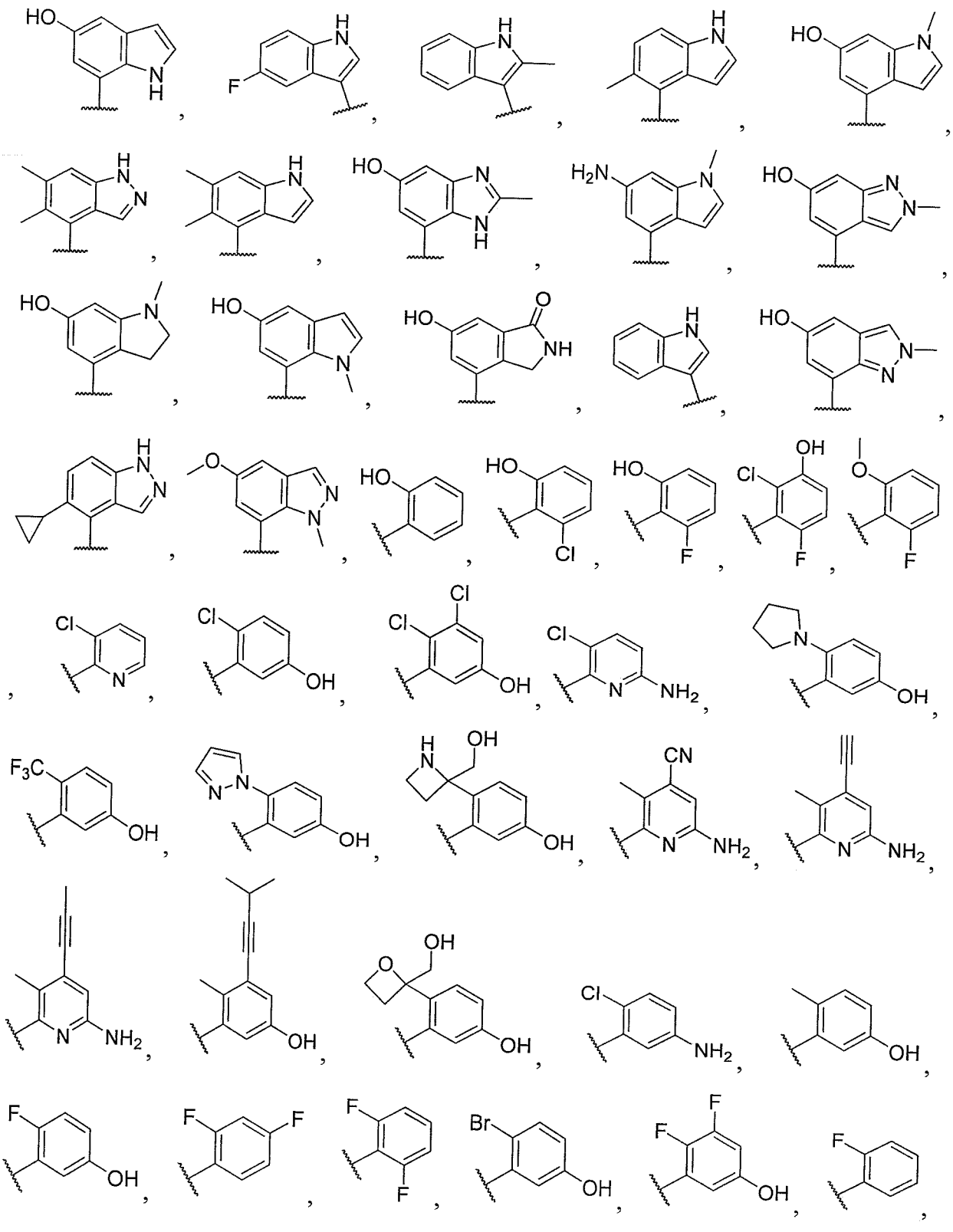


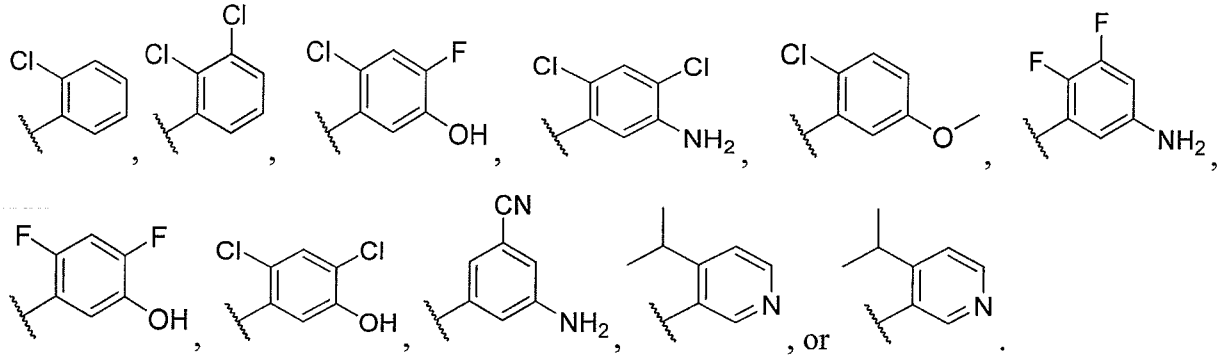
[0023] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some examples, R^1 is H. In some examples, R^1 is F. In some examples, R^1 is methyl.

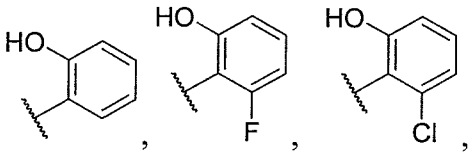
[0024] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various examples, R^2 is aryl. In some examples, R^2 is heteroaryl. In various examples, R^2 is phenyl, naphthyl, pyridyl, indazolyl, indolyl, azaindolyl, indolinyl, benzotriazolyl, benzoxadiazolyl, imidazolyl, cinnolinyl, imidazopyridyl, pyrazolopyridyl, quinolinyl, isoquinolinyl, quinazolinyl,

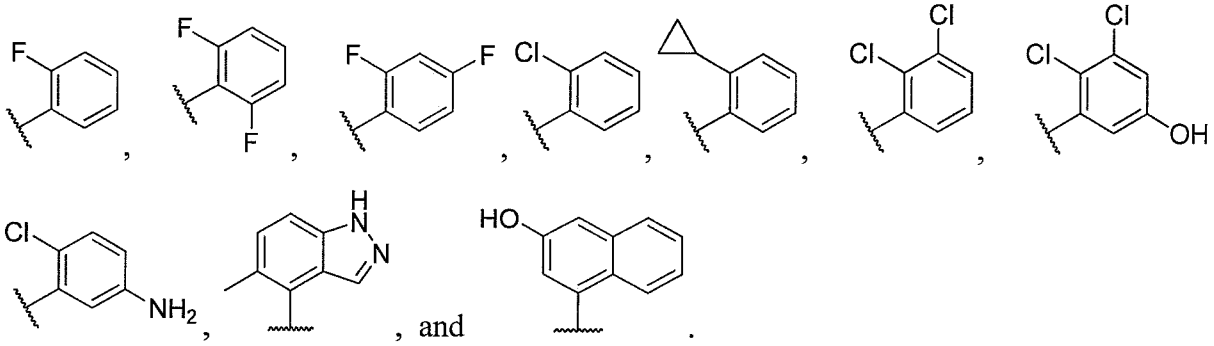
quinazolinonyl, indolinonyl, isoindolinonyl, tetrahydronaphthyl, tetrahydroquinolinyl, or tetrahydroisoquinolinyl. For example, R^2 can be Cl, Br, CF_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidine, pyrrolidine, azetidine, OCH_3, OCH_2CH_3, phenyl,



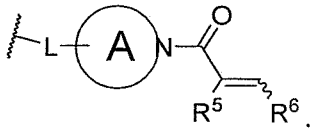
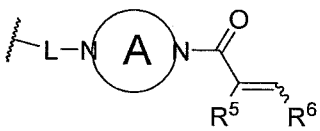
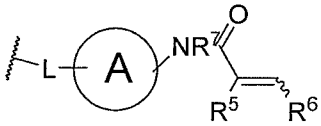
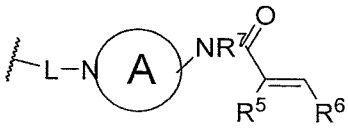
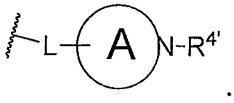


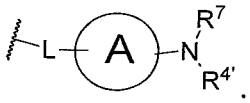
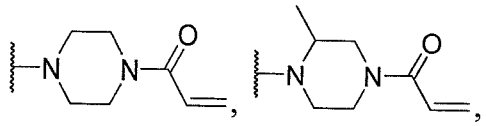
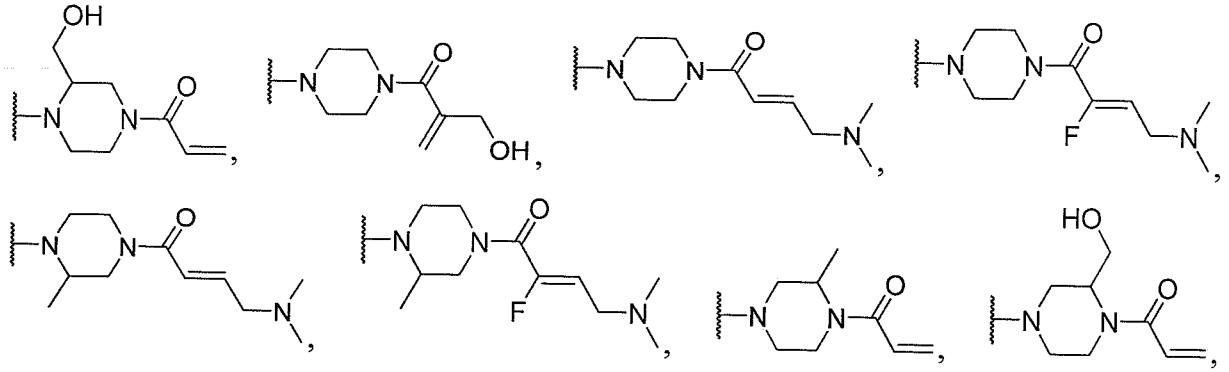
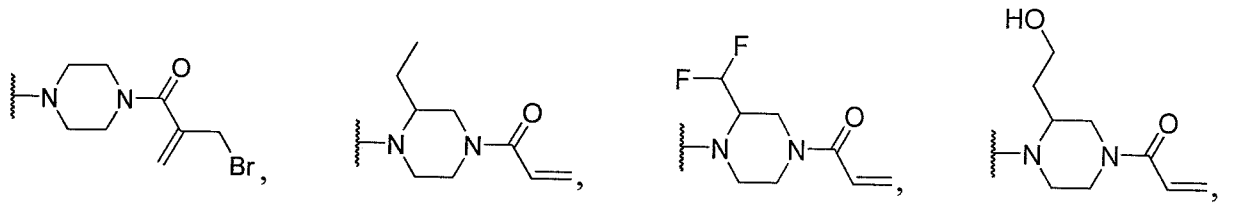
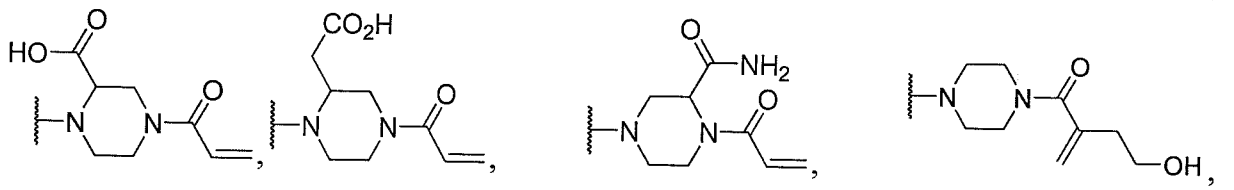
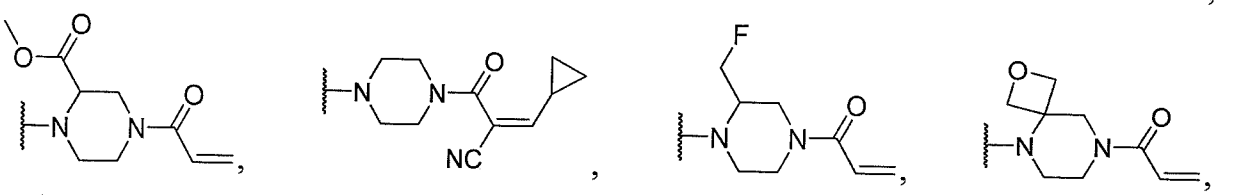
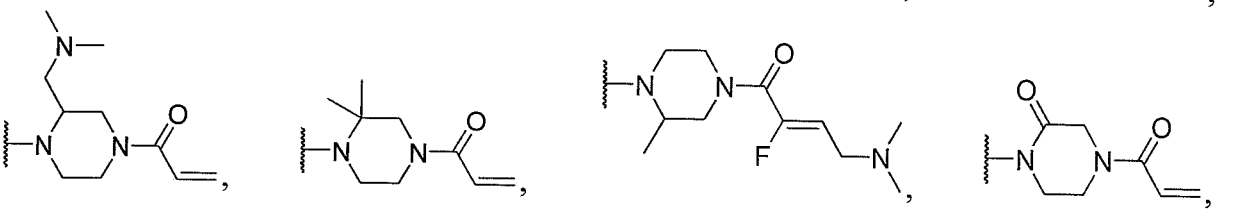
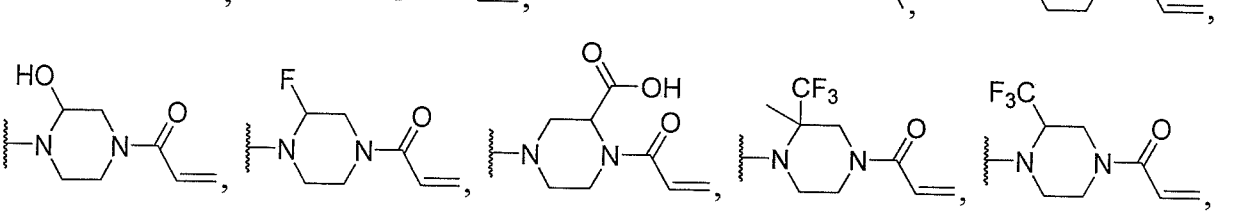
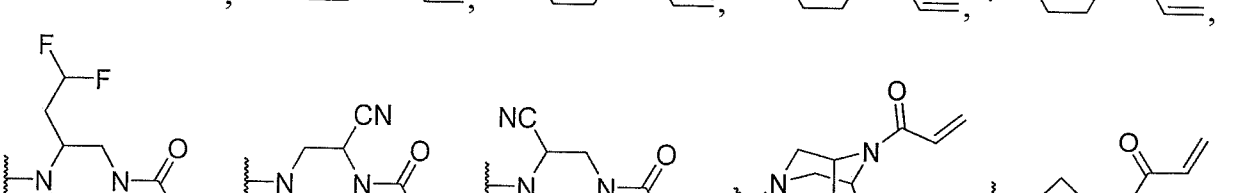
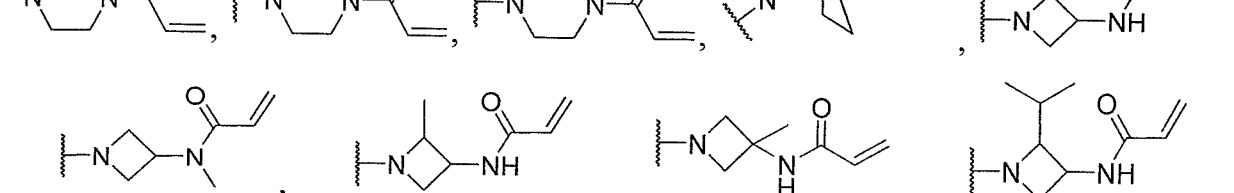
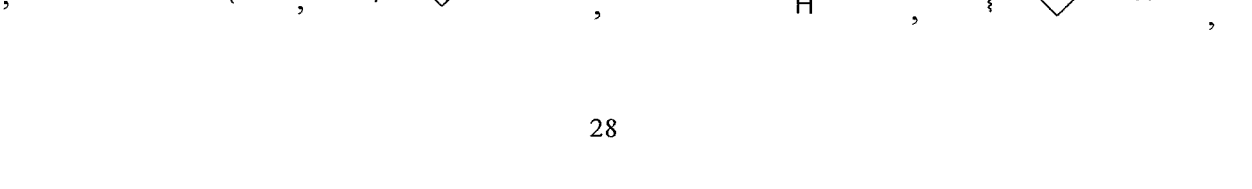


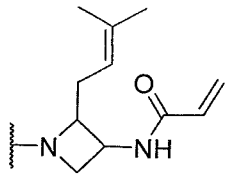
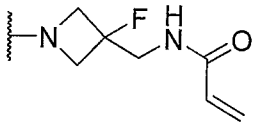
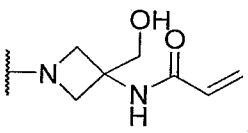
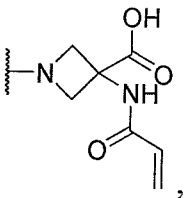
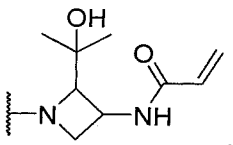
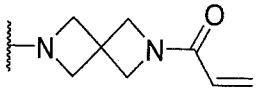
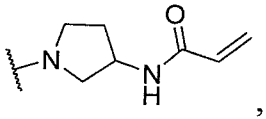
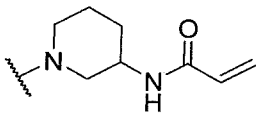
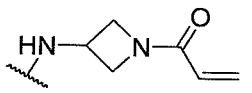
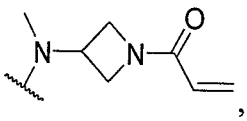
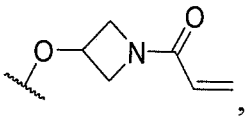
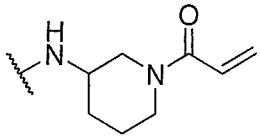
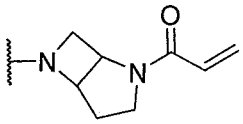
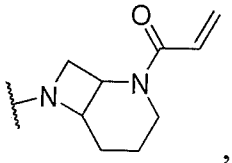
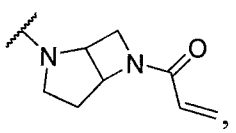
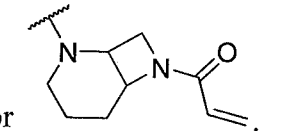
[0025] In various examples, R^2 can be bromine, 

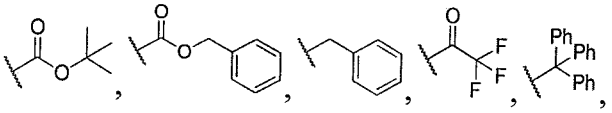


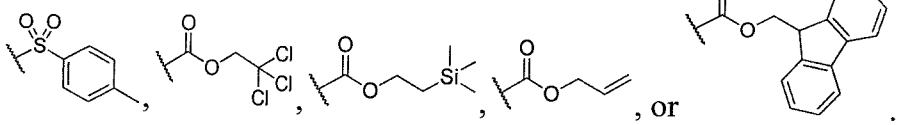
[0026] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various examples, R^3 is halo. In various examples, R^3 is Cl. In various examples, R^3 is F. In some examples, R^3 is C_{1-2}alkyl. In some examples, R^3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

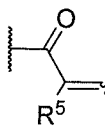
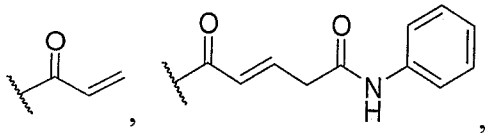
[0027] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some examples, R^4 is . In various examples, R^4 is . In some examples, R^4 is . In some examples, R^4 is . In some examples, R^4 is . In some examples,

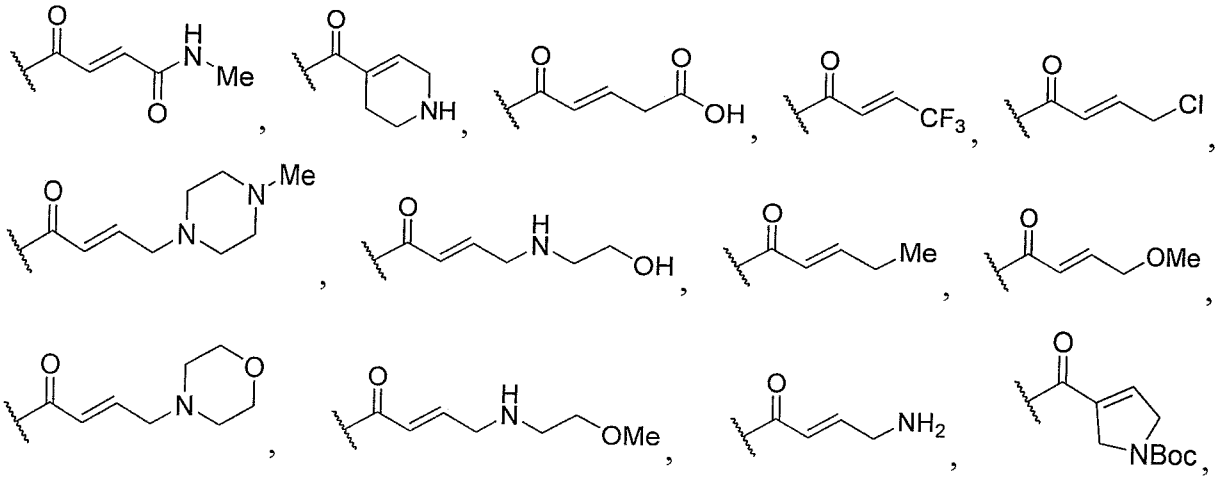
R^4 is . In some examples, R^4 can be , , , , , , , , , , ,

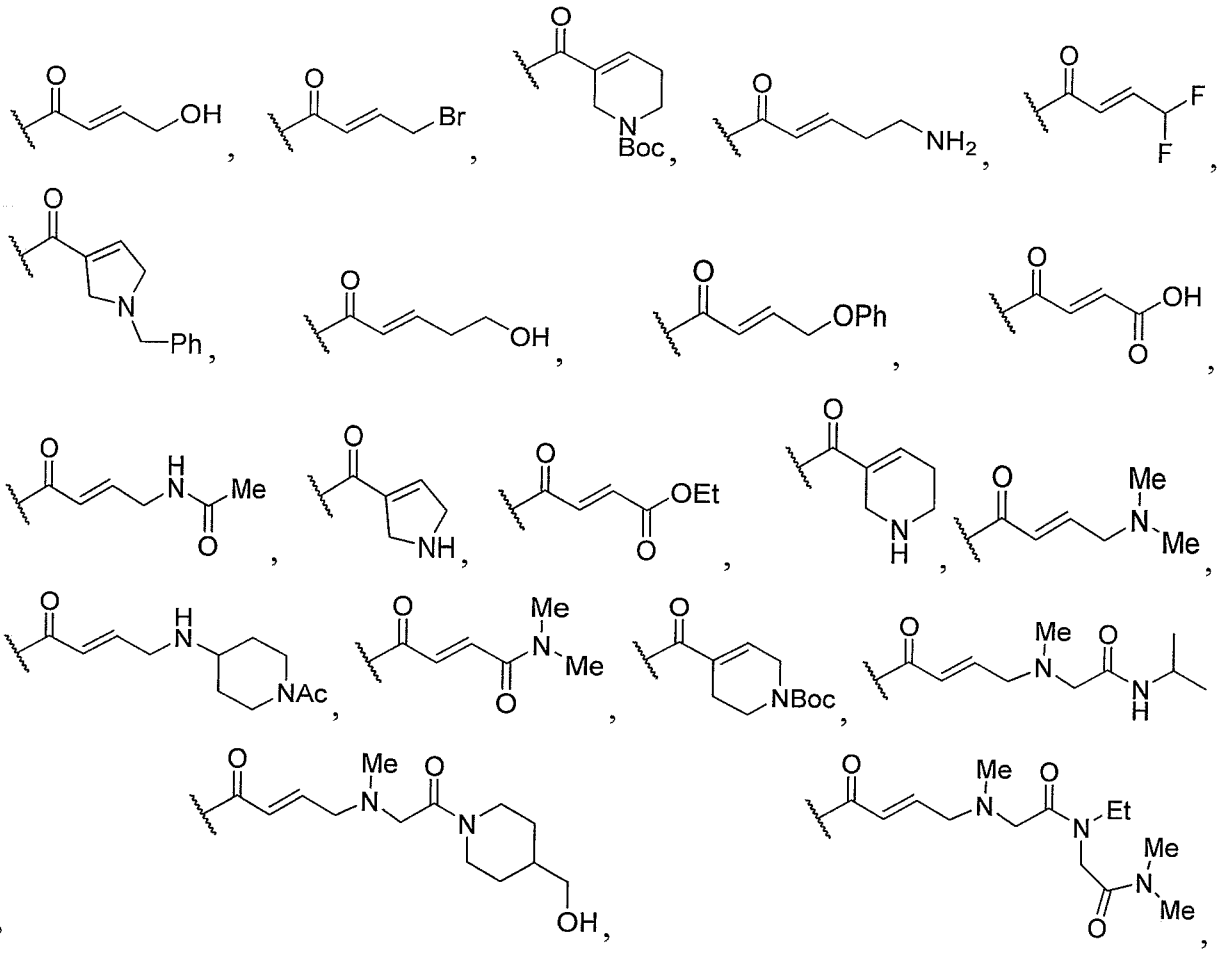

















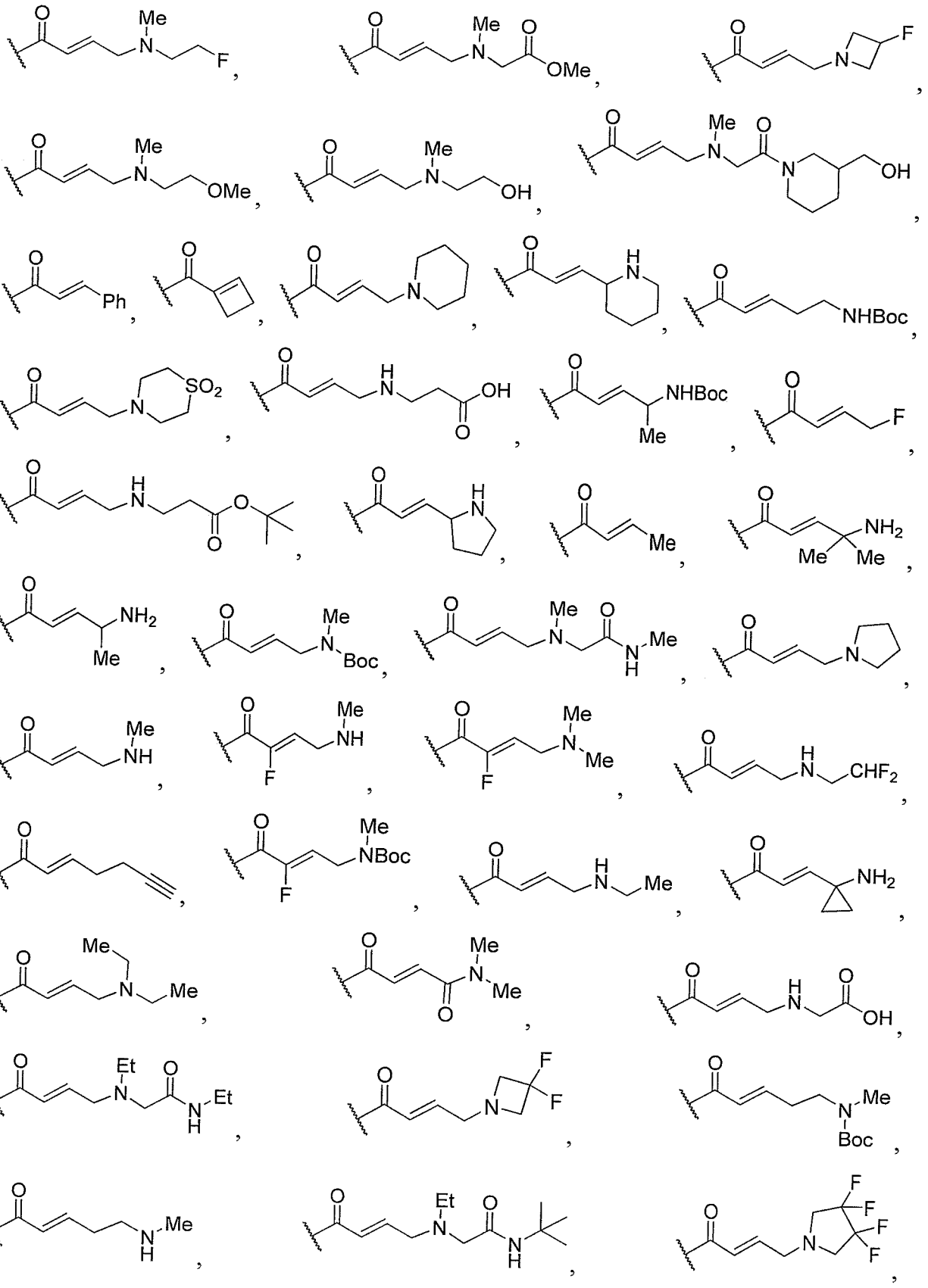
[0028] In various examples $R^{4'}$ is H, C_{1-8}alkyl, C_{2-8}alkynyl, C_{1-6}alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6}haloalkyl, C_{0-3}alkylene-C_{3-8}cycloalkyl, C_{0-3}alkylene-C_{2-7}heterocycloalkyl, C_{0-3}alkylene-C_{6-14}aryl, or selected from 

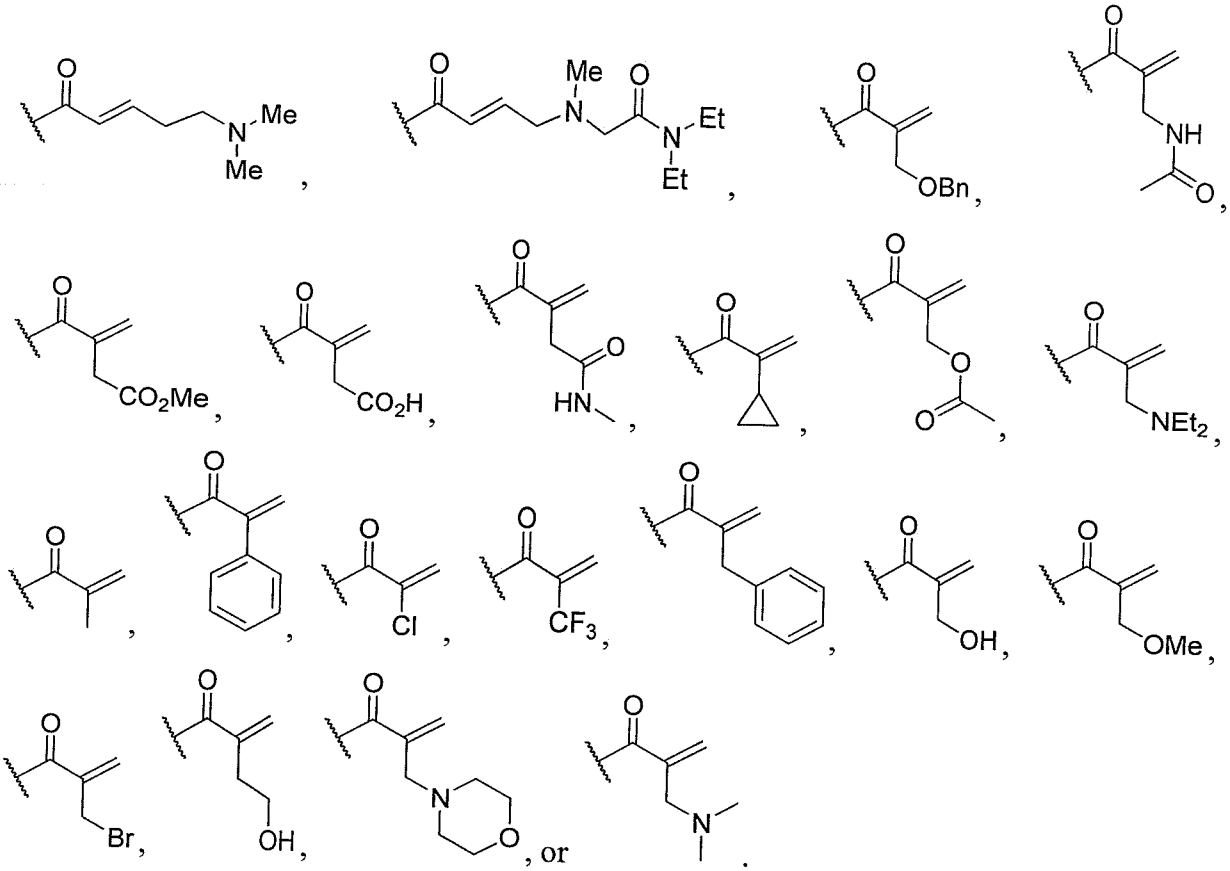


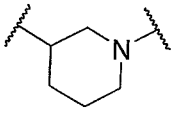
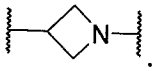
[0029] In various examples,  can be 



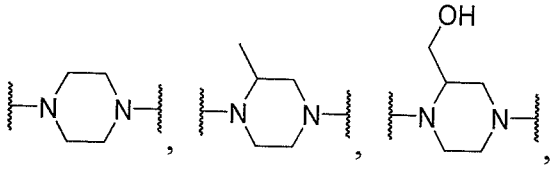


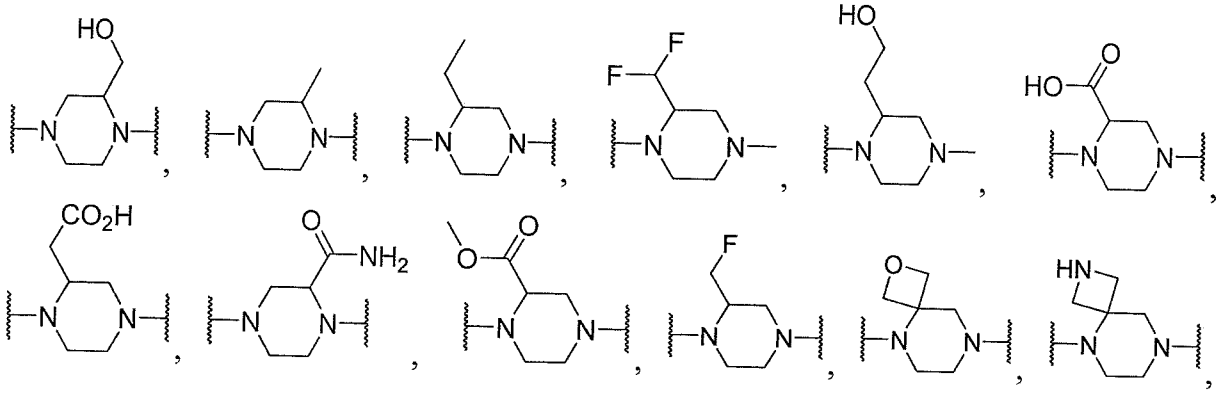


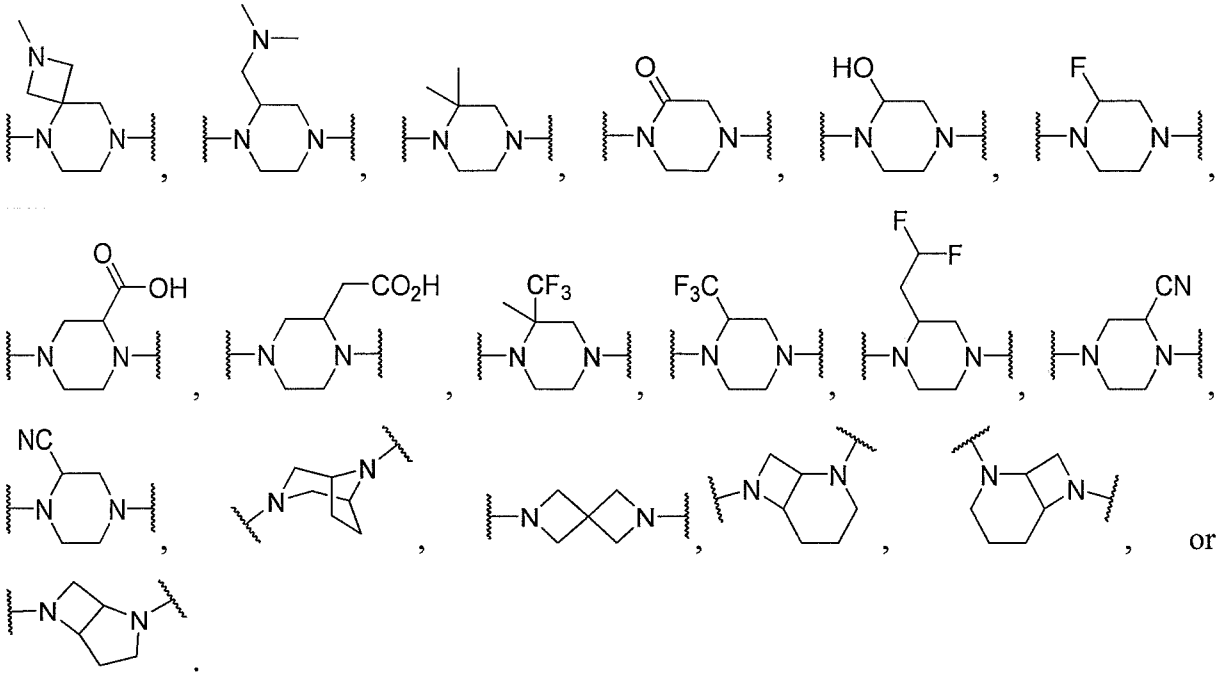


[0030] In some examples, ring A is  or .

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

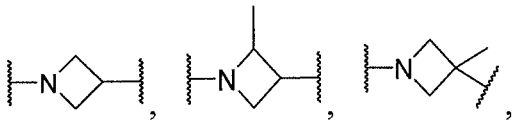
[0032] In various examples, ring A can be 

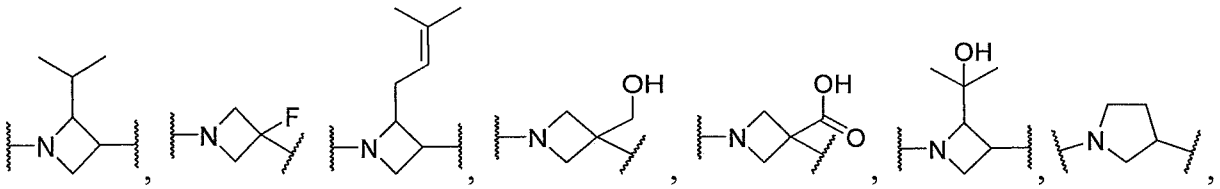


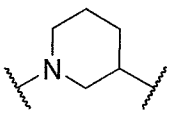


or

.

[0033] In various examples, 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.

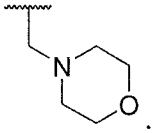
[0035] In some examples, L is a bond.

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

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

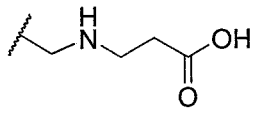
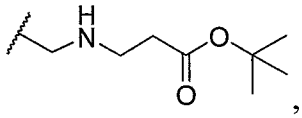
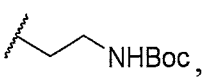
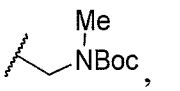
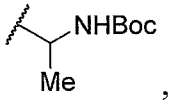
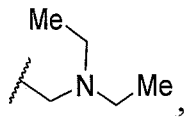
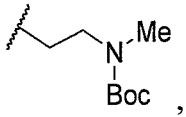
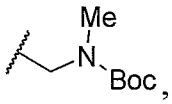
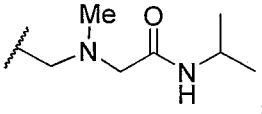
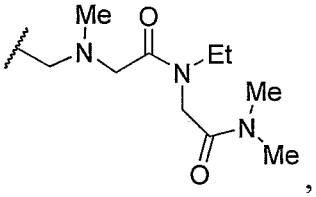
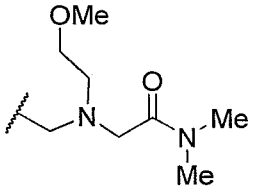
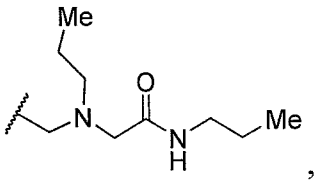
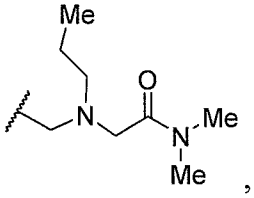
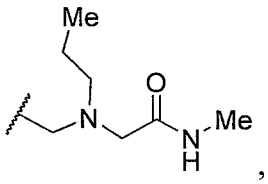
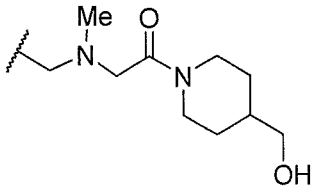
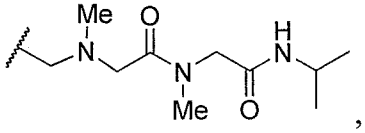
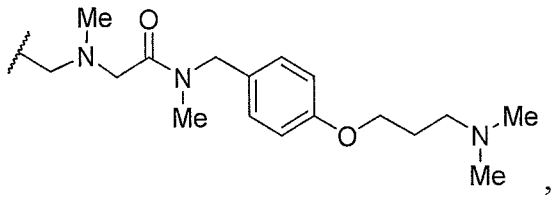
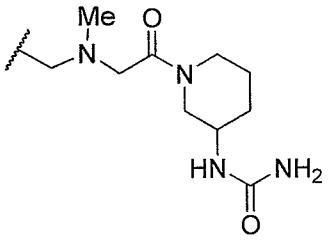
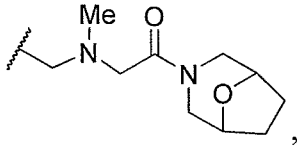
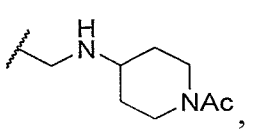
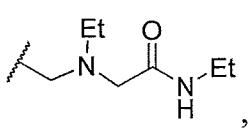
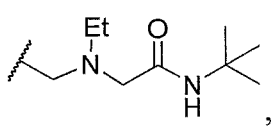
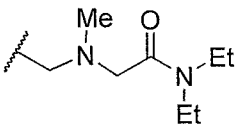
[0038] In various examples, L is NH.

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

[0040] In some examples, 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 .

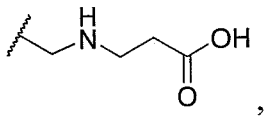
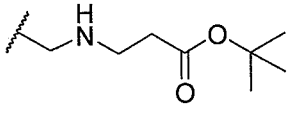
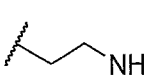
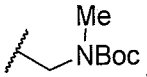
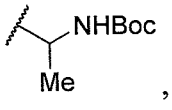
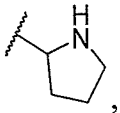
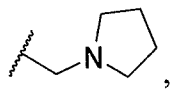
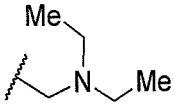
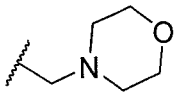
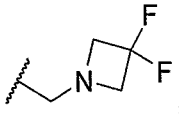
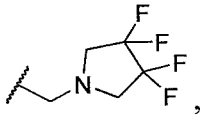
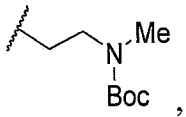
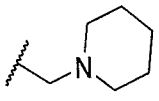
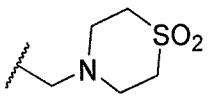
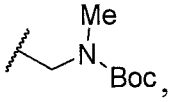
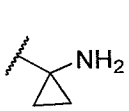
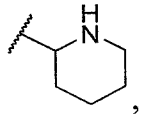
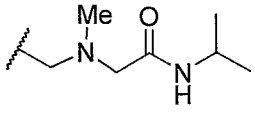
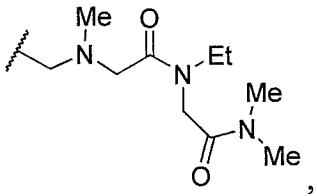
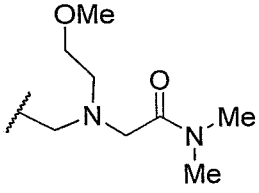
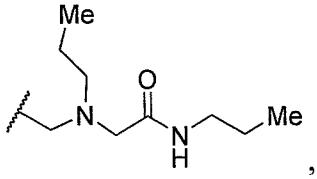
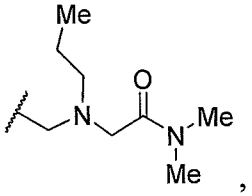
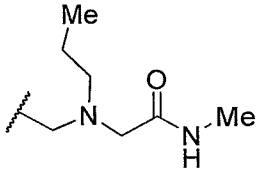
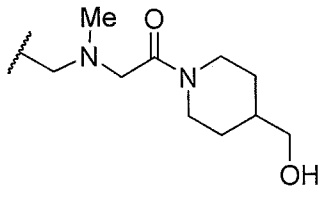
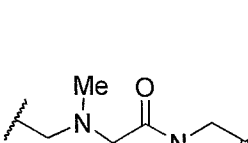
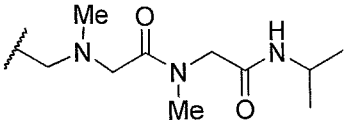
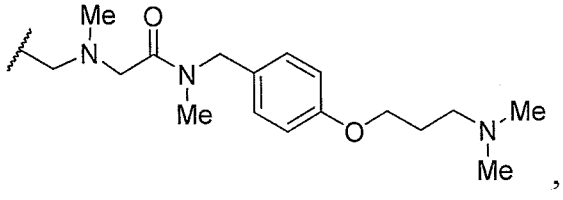
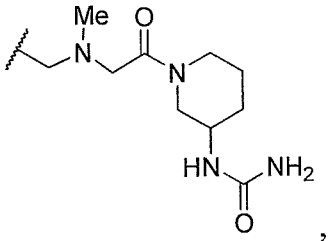
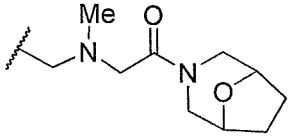
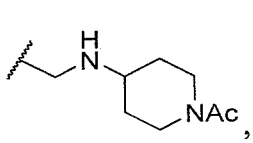
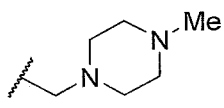
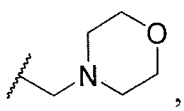
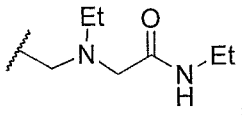
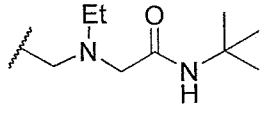
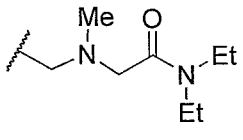
[0041] In some examples, R^6 is C_{1-6}alkyl, C_{1-6}alkylene-O-C_{1-6}alkyl, C_{1-6}alkylene-OH, C_{1-3}haloalkyl, C_{1-6}alkylene-amine, C_{0-6}alkylene-amide, C_{0-1}alkylene $C(O)OC_{1-3}$alkyl, C_{0-1}alkylene-C_{2-14}heterocycloalkyl, C_{0-1}alkylene-C_{3-14}cycloalkyl, or C_{0-3}alkylene-C_{6-14}aryl.

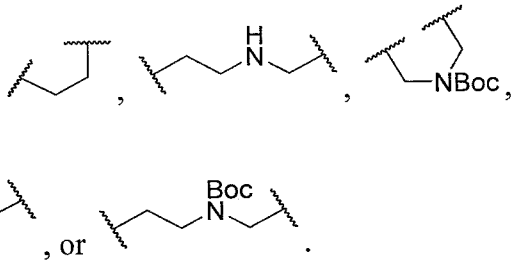
[0042] In various examples, R^6 is C_{0-6}alkylene-amine or C_{0-3}alkylene-amide and is CH_2NH_2, $CH(CH_3)NH_2$, $CH(CH_3)_2NH_2$, $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, CH_2NHCH_3, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $CH_2C(O)NH$phenyl, $CH_2NHC(O)CH_3$, $CH_2NHCH_2CH_2OH$, $CH_2NHCH_2CO_2H$, $CH_2NH(CH_3)CH_2CO_2CH_3$,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


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

, or

.

[0043] In various examples, 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, $CH_2NH(CH_3)CH_2CH_2OH$, $CH_2NH(CH_3)CH_2CH_2F$, $CH_2N^+(CH_3)_3$, $CH_2NHCH_2CHF_2$, $CH_2NHCH_2CH_3$,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

, or

.

[0044] In various examples, R^5 and R^6 together are 

, or .

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

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

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

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

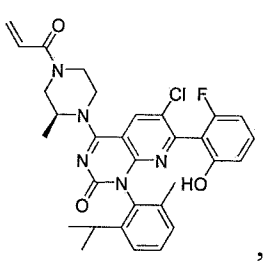
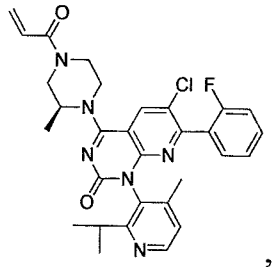
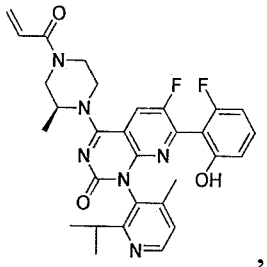
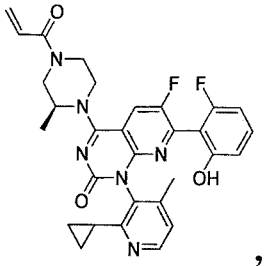
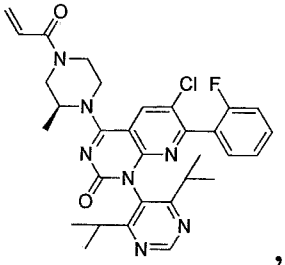
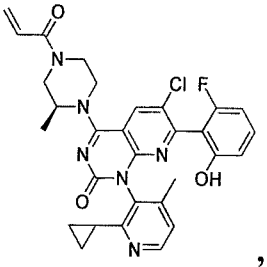
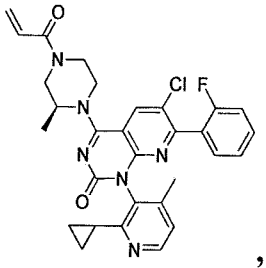
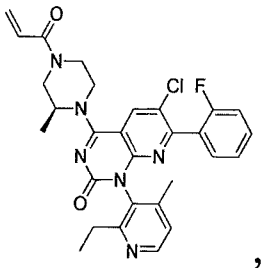
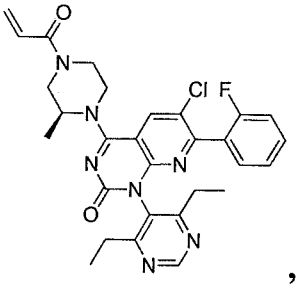
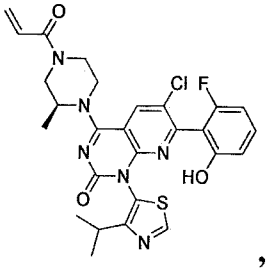
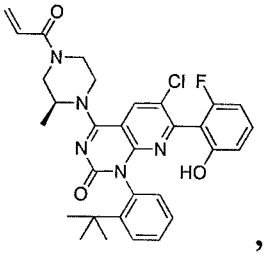
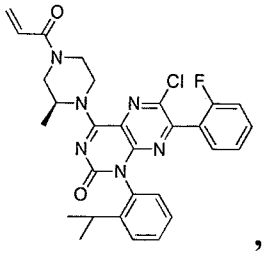
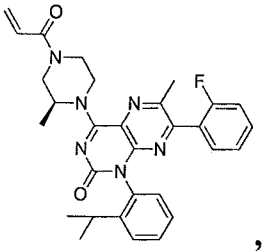
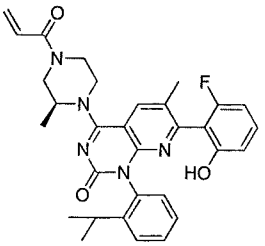
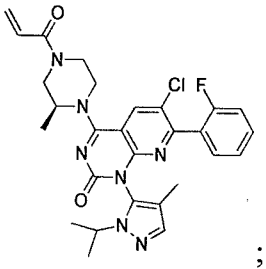
[0049] The compounds disclosed herein can be in the form of a pharmaceutically acceptable salt. The compounds provided can be formulated into a pharmaceutical formulation comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

[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 examples, the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

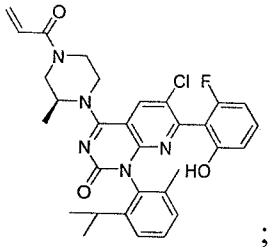
CLAIMS

What is claimed is:

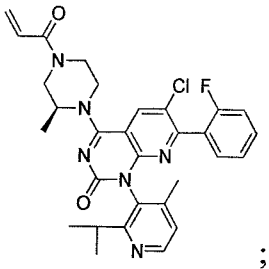
1. A compound having a structure selected from:


,

,

,

,

,

,

,

,

,

,

,

,

,

and

;

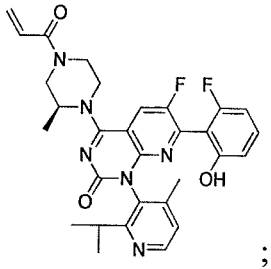
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

2. A compound having a structure  ;

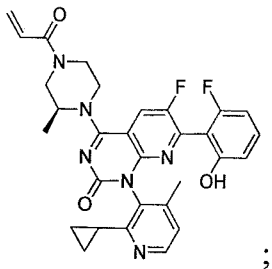
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

3. A compound having a structure  ;

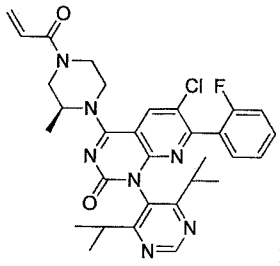
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

4. A compound having a structure  ;

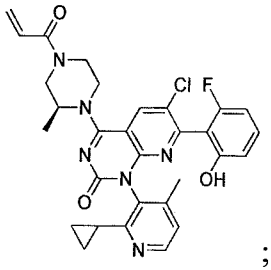
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

5. A compound having a structure  ;

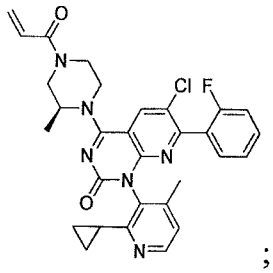
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

6. A compound having a structure  ;

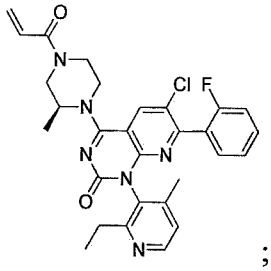
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

7. A compound having a structure  ;

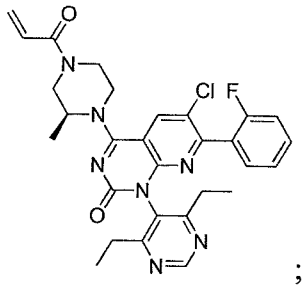
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

8. A compound having a structure  ;

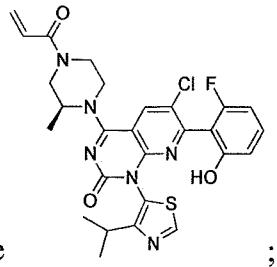
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

9. A compound having a structure  ;

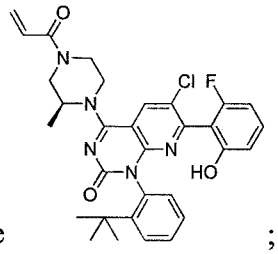
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

10. A compound having a structure  ;

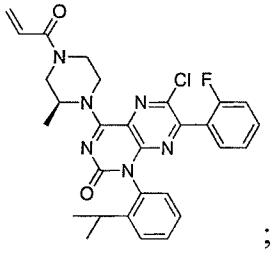
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

11. A compound having a structure  ;

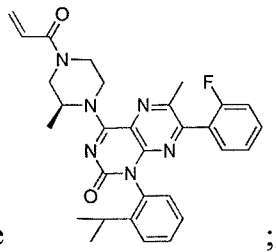
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

12. A compound having a structure  ;

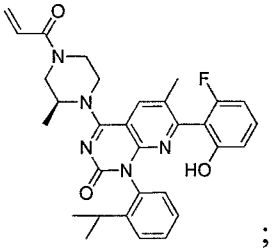
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

13. A compound having a structure  ;

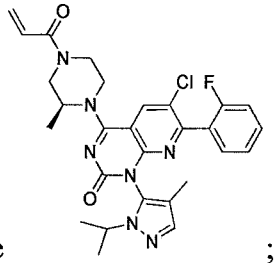
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

14. A compound having a structure  ;

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

15. A compound having a structure  ;

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

16. A compound having a structure  ;

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

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

18. A pharmaceutical formulation comprising any one or more of the compounds of claims 1-17 and a pharmaceutically acceptable excipient.

19. An *in vitro* method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 1-17 or the composition of claim 18.

20. Use of the compound of any one of claims 1-17 or the composition of claim 18 in the manufacture of a medicament for treating cancer in a subject.

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

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

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

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

25. The use of claim 20, further comprising that an additional pharmaceutically active compound is to be administered to the patient.

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

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

28. A compound according to any one of Claims 1-16 for use in treating cancer.

29. The compound according to Claim 28, wherein the cancer is a hematologic malignancy.