

**BENZISOTHIAZOLE, ISOTHIAZOLO[3,4-B]PYRIDINE, QUINAZOLINE,
PHTHALAZINE, PYRIDO[2,3-D]PYRIDAZINE AND PYRIDO[2,3-D]PYRIMIDINE
DERIVATIVES AS KRAS G12C INHIBITORS FOR TREATING LUNG,
PANCREATIC OR COLORECTAL CANCER
RELATED APPLICATIONS**

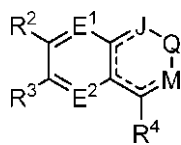
This application claims the benefit of U.S. Provisional patent application 62/438,334 filed on December 22, 2016, which specification is hereby incorporated herein by reference in its entirety for all purposes.

BACKGROUND

[0001] 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 patients 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

[0001a] In one aspect, the present disclosure refers to a compound having a structure of formula (II)



wherein

E¹ and E² are each independently N or CR¹;

J is N, NR¹⁰, or CR¹⁰;

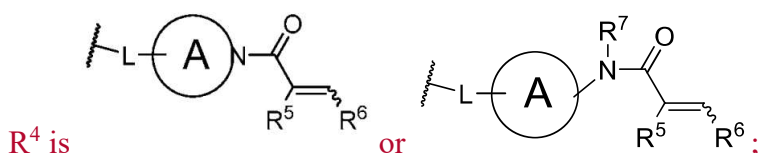
M is N, NR¹³, or CR¹³;

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

R¹ is independently H, hydroxy, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, NH-C₁₋₄alkyl, N(C₁₋₄alkyl)₂, cyano, or halo;

R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₃₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R³ is halo, C₁₋₃alkyl, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₄cycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;



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

L is a bond, C₁₋₆alkylene, -O-C₀₋₅alkylene, -S-C₀₋₅alkylene, or -NH-C₀₋₅alkylene, and for C₂₋₆alkylene, -O-C₂₋₅alkylene, -S-C₂₋₅alkylene, or -NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₆alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₁₋₆alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring;

R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4-6 membered ring;

Q is CR⁸R⁹, C=CR⁸R⁹, C=O, C=S, or C=NR⁸;

R⁸ and R⁹ are each independently H, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, cyano, nitro, or C₃₋₆cycloalkyl, or R⁸ and R⁹, taken together with the carbon atom to which they are attached, can form a 3-6 membered ring;

R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; and

R¹³ is C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, or C₃₋₁₄cycloalkyl; or

a pharmaceutically acceptable salt thereof,

with the proviso that

(1) when J is NR¹⁰, M is N or CR¹³;

(2) when M is NR¹³, J is N or CR¹⁰;

(3) when J is CR¹⁰, M is N or NR¹³; and

(4) when M is CR¹³, J is N or NR¹⁰;

wherein

an alkyl, alkylene, alkenyl, alkynyl or alkoxy group is optionally substituted with one or more groups independently selected from halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -NC, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl;

an aryl group is unsubstituted or optionally substituted with one or more groups independently selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -CF₃, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl;

a cycloalkyl or heterocycloalkyl group is unsubstituted or optionally substituted with one or more groups selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl; and

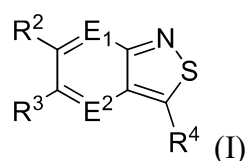
a heteroaryl group is unsubstituted or optionally substituted with one or more substituents selected from halo, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OCF₃, -NO₂, -CN, -NC, -OH, alkoxy, amino, -CO₂H, -CO₂C₁₋₈alkyl, -OCOC₁₋₈alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀heterocycloalkyl, C₅₋₁₀aryl, and C₅₋₁₀heteroaryl.

[0001b] In another aspect, the present disclosure refers to a pharmaceutical formulation comprising the compound as disclosed herein and a pharmaceutically acceptable excipient.

[0001c] In yet 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 pharmaceutical formulation as described herein.

[0001d] In yet another aspect, the present disclosure refers to a use of a compound as described herein or the pharmaceutical formulation as described herein in the manufacture of a medicament for treating cancer.

[0002] Provided herein are compound having a structure of formula (I)



wherein

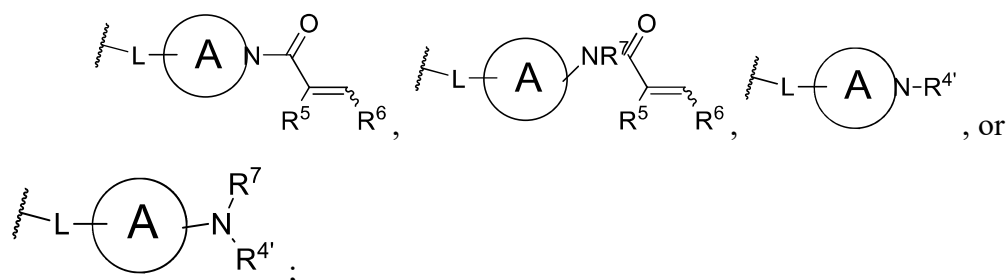
E¹ and E² are each independently N or CR¹;

R¹ is independently H, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, NH-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, cyano, or halo;

R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylenearyl, or C₀₋₃alkyleneheteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R³ is halo, C₁₋₃alkyl, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₄cycloalkyl, C₂₋₃ alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;

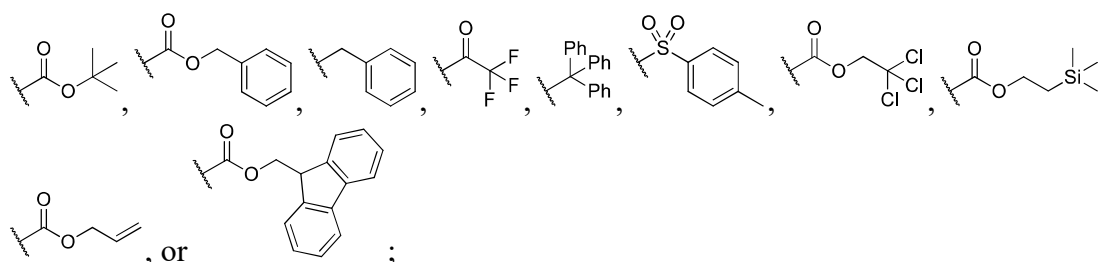
R⁴ is



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

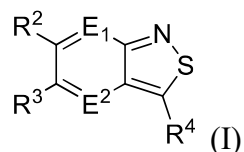
L is a bond, C₁₋₆alkylene, -O-C₀₋₅alkylene, -S-C₀₋₅alkylene, or -NH-C₀₋₅alkylene, and for C₂₋₆alkylene, -O-C₂₋₅alkylene, -S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^{4'} is H, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, cycloalkyl, heterocycloalkyl, C₀₋₃alkylene-C₃₋₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or selected from



R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4–6 membered ring; and

R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4–6 membered ring, or a pharmaceutically acceptable salt thereof.



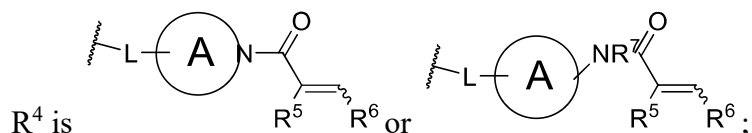
wherein

E^1 and E^2 are each independently N or CR¹;

R¹ is independently H, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, NH-C₁₋₆alkyl, N(C₁₋₄alkyl)₂, cyano, or halo;

R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R³ is halo, C₁₋₃alkyl, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₁₄cycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;



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

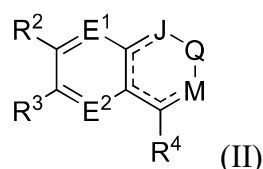
L is a bond, C₁₋₆alkylene, -O-C₀₋₅alkylene, -S-C₀₋₅alkylene, or -NH-C₀₋₅alkylene, and for C₂₋₆alkylene, -O-C₂₋₅alkylene, -S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R⁵ and R⁶ are each independently H, halo, C₁₋₈alkyl, C₂₋₈alkynyl, C₁₋₆ alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆ alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆ alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring; and

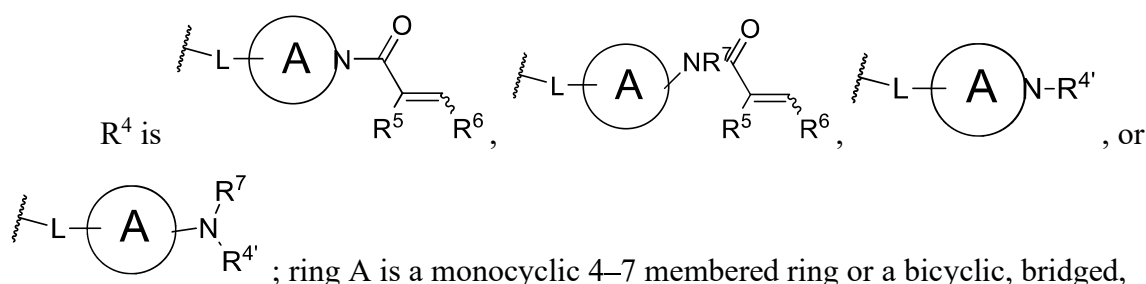
R^7 is H or C_{1-6} alkyl, or R^7 and R^5 , together with the atoms to which they are attached,

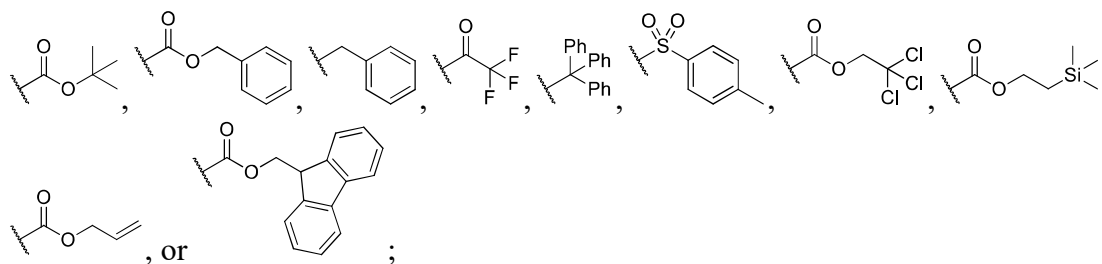
form a 4–6 membered ring,
or a pharmaceutically acceptable salt thereof.

[0004] Further provided are compounds of formula (II), or a pharmaceutically acceptable salt thereof:



wherein E¹ and E² are each independently N or CR¹; J is N, NR¹⁰, or CR¹⁰; M is N, NR¹³, or CR¹³; == is a single or double bond as necessary to give every atom its normal valence; R¹ 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; R² 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; R³ 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;



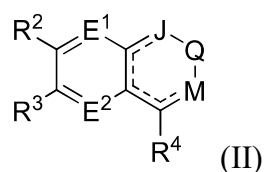


R^5 and R^6 are each independently H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} alkylene-O- C_{1-4} alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, C_{1-6} alkyleneamine, C_{0-6} alkylene-amide, C_{0-3} alkylene-C(O)OH, C_{0-3} alkylene-C(O)OC $_{1-4}$ alkyl, C_{1-6} alkylene-O-aryl, C_{0-3} alkylene-C(O)C $_{1-4}$ 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 ^{8} R ^{9} , C=CR ^{8} R ^{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} .

[0005] In some **embodimentexamples**, 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 **embodimentexamples**, J is NR ^{10} and M is CR ^{13} . In some **embodimentexamples**, J is CR ^{10} and M is NR ^{13} . In some **embodimentexamples**, J is N and M is NR ^{13} . In various **embodimentexamples**, J is NR ^{10} and M is N.

[0006] Further provided are compounds having a structure of formula (II)



wherein

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

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

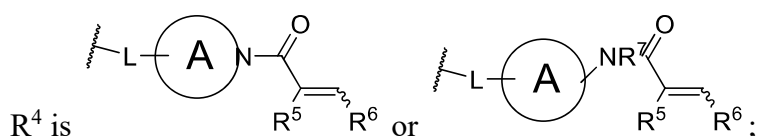
M is N, NR^{13} , or CR^{13} ;

== 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;



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;

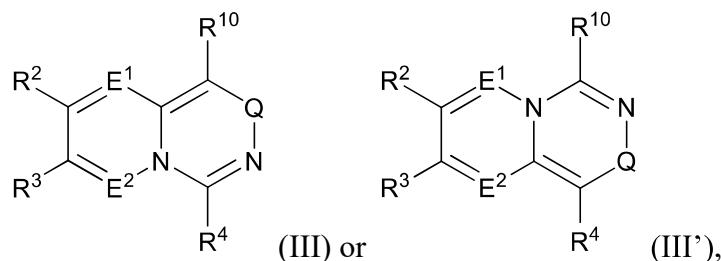
R^{10} is C_{1-8} alkyl, C_{0-3} alkylene- C_{6-14} aryl, C_{0-3} alkylene- C_{3-14} heteroaryl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14} heterocycloalkyl, C_{1-6} alkoxy, O- C_{0-3} alkylene- C_{6-14} aryl, O- C_{0-3} alkylene- C_{3-14} heteroaryl, O- C_{0-3} alkylene- C_{3-14}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

[0007] In some [embodimentexamples](#), 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 [embodimentexamples](#), J is NR^{10} and M is CR^{13} . In some [embodimentexamples](#), J is CR^{10} and M is NR^{13} . In some [embodimentexamples](#), J is N and M is NR^{13} . In various [embodimentexamples](#), J is NR^{10} and M is N.

[0008] Further provided are compounds of formula (III) or (III'), or a pharmaceutically acceptable salt thereof:



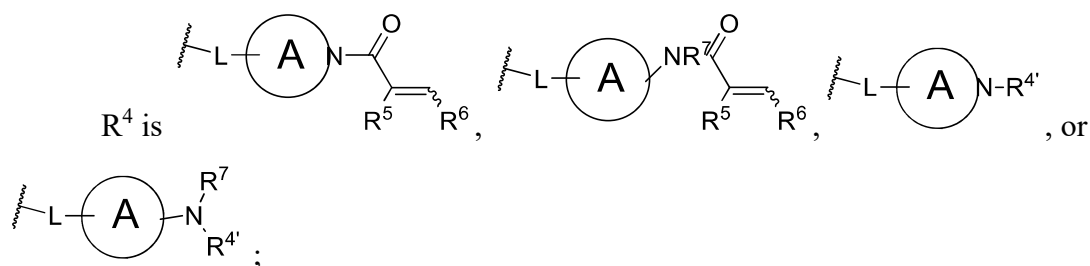
wherein E^1 and E^2 are each independently N or CR^1 ;

R^1 is independently H, hydroxy, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, NH- C_{1-4} alkyl,

$N(C_{1-4}\text{alkyl})_2$, cyano, or halo;

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

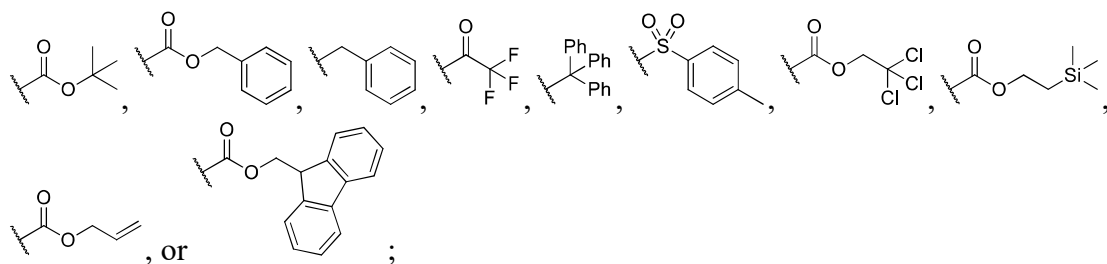
R^3 is halo, $C_{1-3}\text{alkyl}$, $C_{1-2}\text{haloalkyl}$, $C_{1-3}\text{alkoxy}$, $C_{3-4}\text{cycloalkyl}$, $C_{2-14}\text{heterocycloalkyl}$, $C_{2-3}\text{alkenyl}$, $C_{2-3}\text{alkynyl}$, aryl, or heteroaryl;



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

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

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



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

form a 4–6 membered ring;

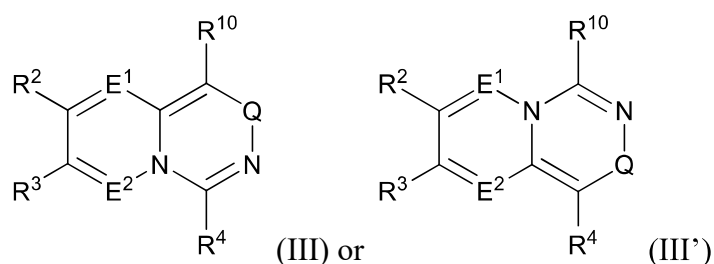
R^7 is H or C_{1-8} alkyl, or R^7 and R^5 , together with the atoms to which they are attached, form a 4–6 membered ring;

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.

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



wherein

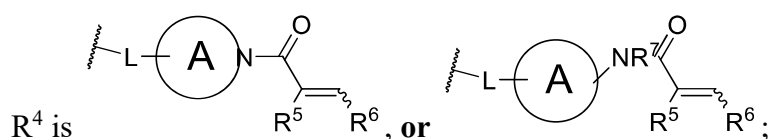
E^1 and E^2 are each independently N or CR^1 ;

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,

C₂₋₃ alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;



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

L is a bond, C₁₋₆alkylene, -O-C₀₋₅alkylene, -S-C₀₋₅alkylene, or -NH-C₀₋₅alkylene, and for C₂₋₆alkylene, -O-C₂₋₅alkylene, -S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4–6 membered ring;

R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4–6 membered ring;

Q is CR⁸R⁹, C=CR⁸R⁹, C=O, C=S, or C=NR⁸;

R⁸ and R⁹ are each independently H, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, cyano, nitro, or C₃₋₁₄cycloalkyl, or R⁸ and R⁹, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

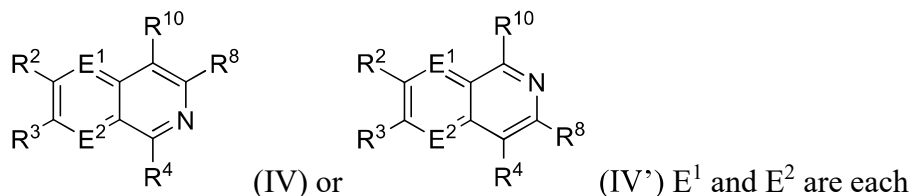
R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine.

[0010] In some [embodimentexamples](#), the compounds have a structure of formula (III). In other [embodimentexamples](#), the compounds have a structure of formula (III').

[0011] The compounds of formula (II) or (III) as disclosed herein can have one or more of the following features. In some [embodimentexamples](#), Q is C=O. In some [embodimentexamples](#), Q is C=S. In some [embodimentexamples](#), Q is C=NR⁸. In various [embodimentexamples](#), R⁸ is C₁₋₂alkyl. In some

embodiment examples, Q is CR⁸R⁹. In various embodiment examples, Q is C=CR⁸R⁹. In some embodiment examples, R⁸ and R⁹, taken together with the carbon atom to which they are attached, form a 3–4 membered ring. In some embodiment examples, R⁸ is C_{1–2}alkyl, and R⁹ is H.

[0012] Also provided are compounds of formula (IV) or (IV'), or a pharmaceutically acceptable salt thereof:

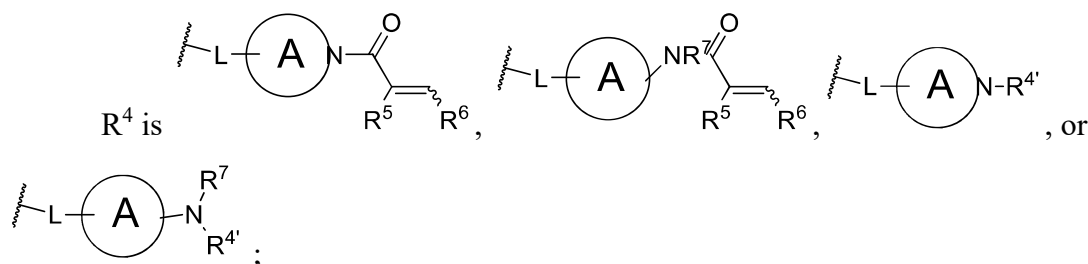


independently CR¹ or N;

R¹ 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;

R² 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;

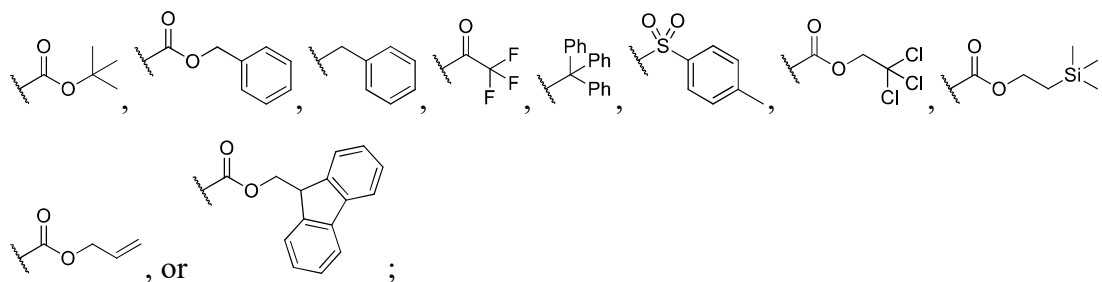
R³ is halo, C_{1–2}haloalkyl, C_{1–3}alkoxy, C_{3–4}cycloalkyl, C_{2–3}alkenyl, C_{2–3}alkynyl, aryl, or heteroaryl;



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;

R⁴ 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, cycloalkyl, 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 $NR^{11}R^{12}$;

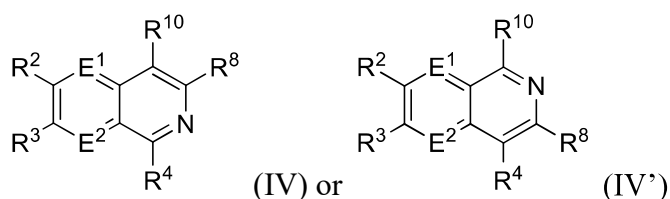
R^{11} and R^{12} are each independently H, C_{1-8} alkyl, or C_{3-14} cycloalkyl; and

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;

[0013] In some [embodimentexamples](#), the compounds disclosed herein have a structure of formula (IV). In various [embodimentexamples](#), the compounds disclosed herein have a structure of formula (IV'). In some [embodimentexamples](#), E^1 and E^2 are each CR^1 , and R^8 is hydroxy, halo, nitro, or C_{3-6} cycloalkyl.

[0014] In some [embodimentexamples](#), R^8 is methyl.

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



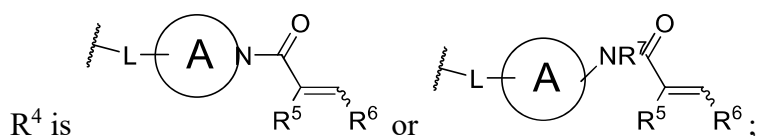
wherein

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;



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

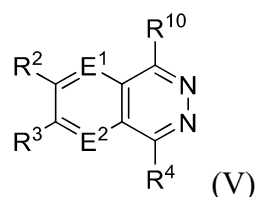
R^{10} is C_{1-8} alkyl, C_{0-3} alkylene- C_{6-14} aryl, C_{0-3} alkylene- C_{3-14} heteroaryl, C_{0-3} alkylene-

C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or a pharmaceutically acceptable salt thereof.

[0015] In some embodiment examples, the compounds disclosed herein have a structure of formula (IV). In various embodiment examples, the compounds disclosed herein have a structure of formula (IV'). In some embodiment examples, E¹ and E² are each CR¹, and R⁸ is hydroxy, halo, nitro, or C₃₋₆cycloalkyl.

[0016] In some embodiment examples, R⁸ is methyl.

[0017] Further provided are compounds having a structure of formula (V), or a pharmaceutically acceptable salt thereof:



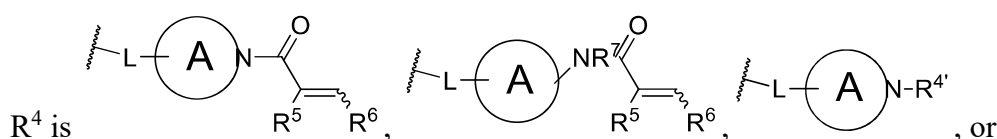
wherein

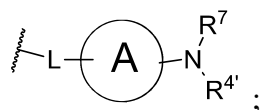
E¹ and E² are each independently CR¹ or N;

R¹ is independently H, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, NH-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, cyano, or halo;

R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R³ is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₁₄cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl, or heteroaryl;

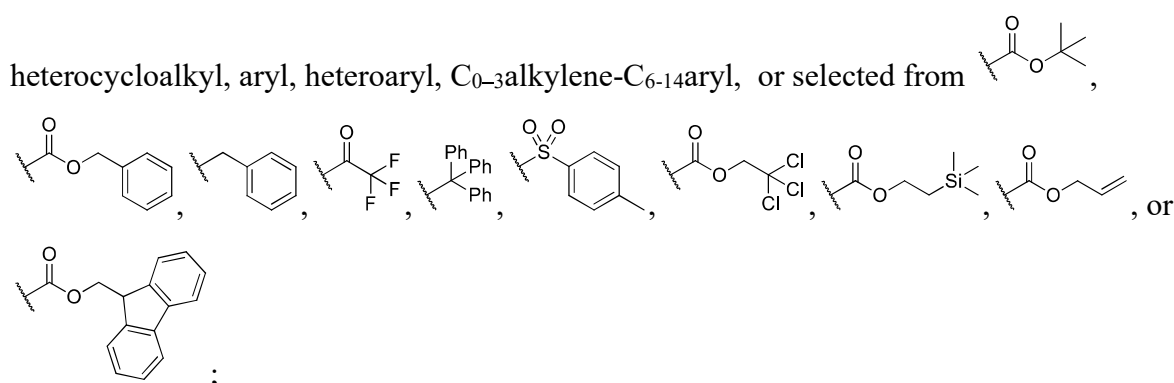




ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, C₁₋₆alkylene, -O-C₀₋₅alkylene, -S-C₀₋₅alkylene, or -NH-C₀₋₅alkylene, and for C₂₋₆alkylene, -O-C₂₋₅alkylene, -S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^{4'} is H, C₁₋₈alkyl, C₂₋₈alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, cycloalkyl, heterocycloalkyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄

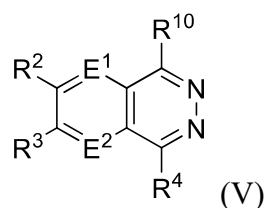


R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4–6 membered ring;

R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4–6 membered ring; and

R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or a pharmaceutically acceptable salt thereof.

[0018] Further provided are compounds having a structure of formula (V):



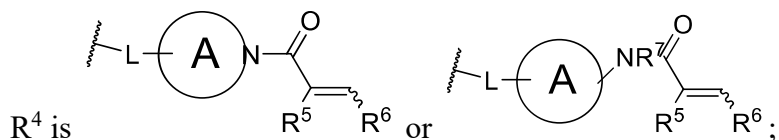
wherein

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;



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;

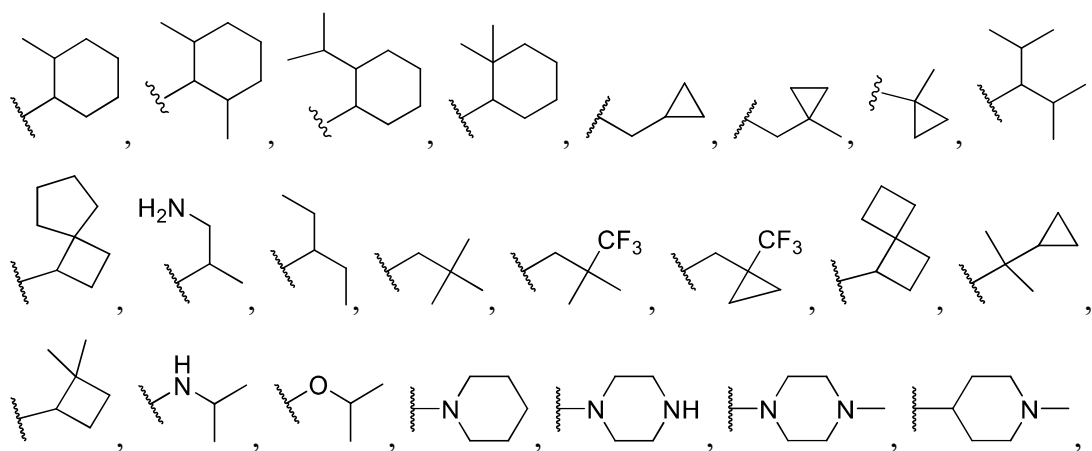
R^5 and R^6 are each independently H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} alkylene- $O-C_{1-4}$ alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, C_{1-6} alkyleneamine, C_{0-6} alkylene-amide, C_{0-3} alkylene- $C(O)OH$, C_{0-3} alkylene- $C(O)OC_{1-4}$ alkyl, C_{1-6} alkylene- O -aryl, C_{0-3}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

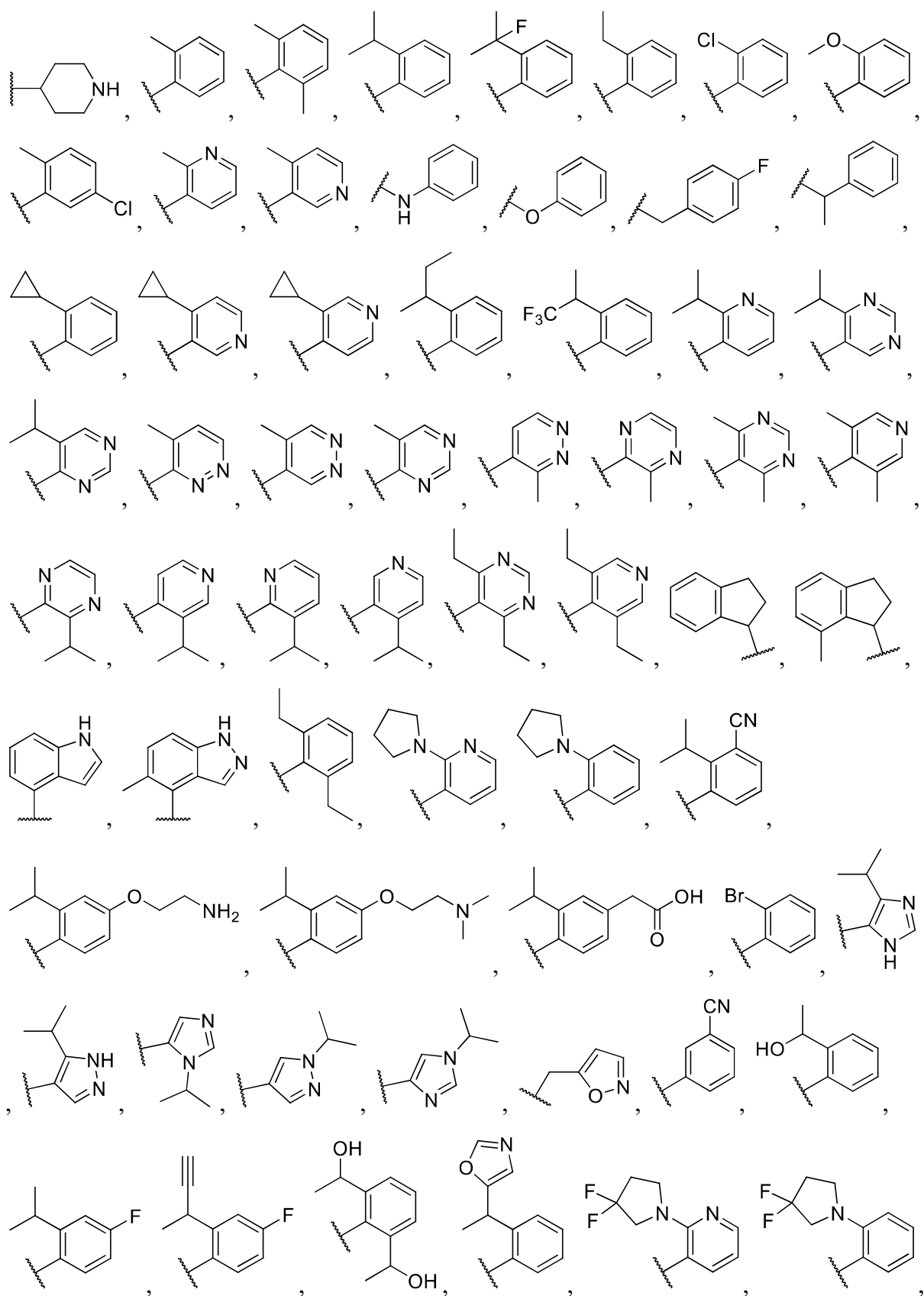
R^7 is H or C_{1-8} alkyl, or R^7 and R^5 , together with the atoms to which they are attached, form a 4–6 membered ring; and

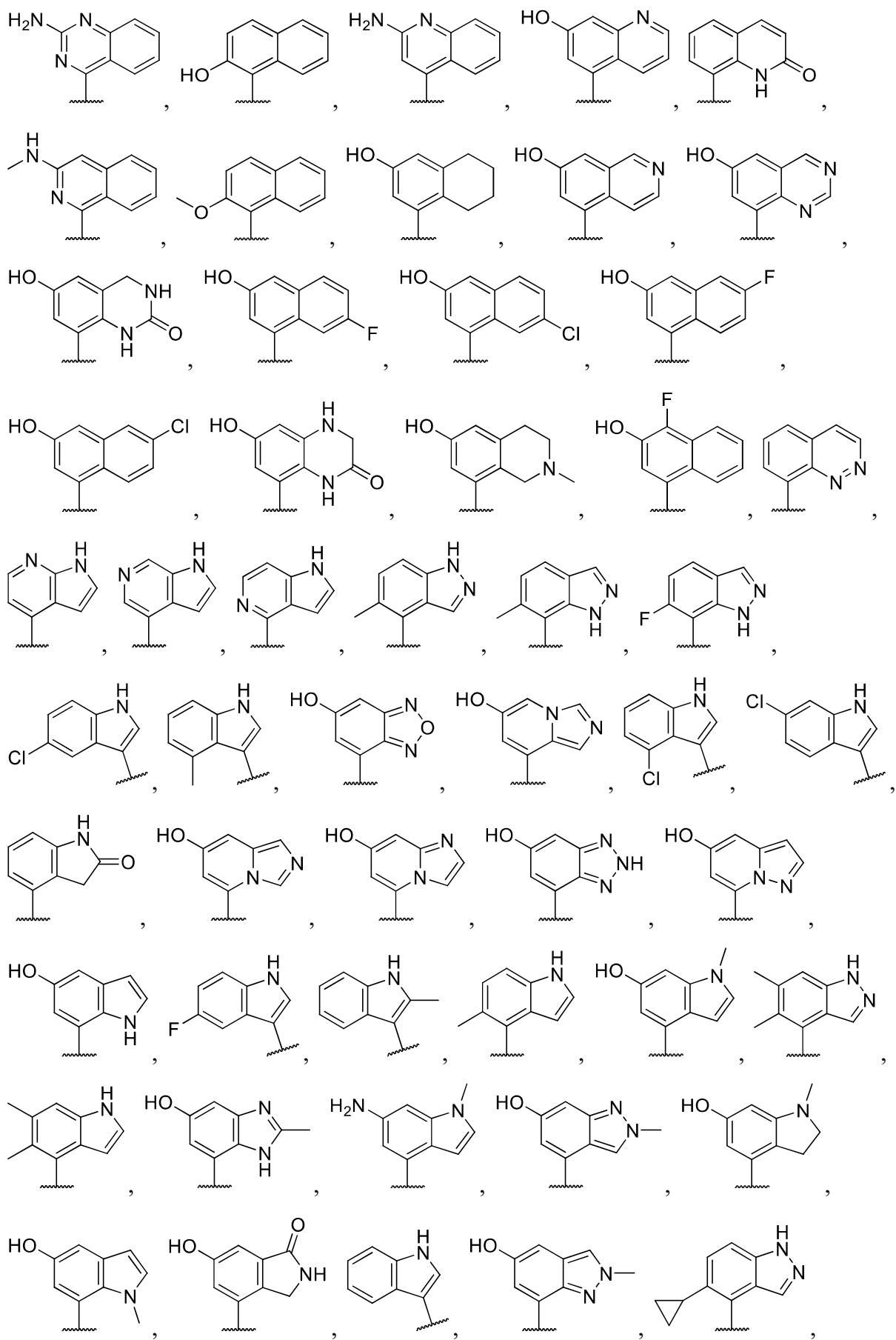
R^{10} is C_{1-8} alkyl, C_{0-3} alkylene- C_{6-14} aryl, C_{0-3} alkylene- C_{3-14} heteroaryl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14} heterocycloalkyl, C_{1-6} alkoxy, O- C_{0-3} alkylene- C_{6-14} aryl, O- C_{0-3} alkylene- C_{3-14} heteroaryl, O- C_{0-3} alkylene- C_{3-14} 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} alkyleneamine; or a pharmaceutically acceptable salt thereof.

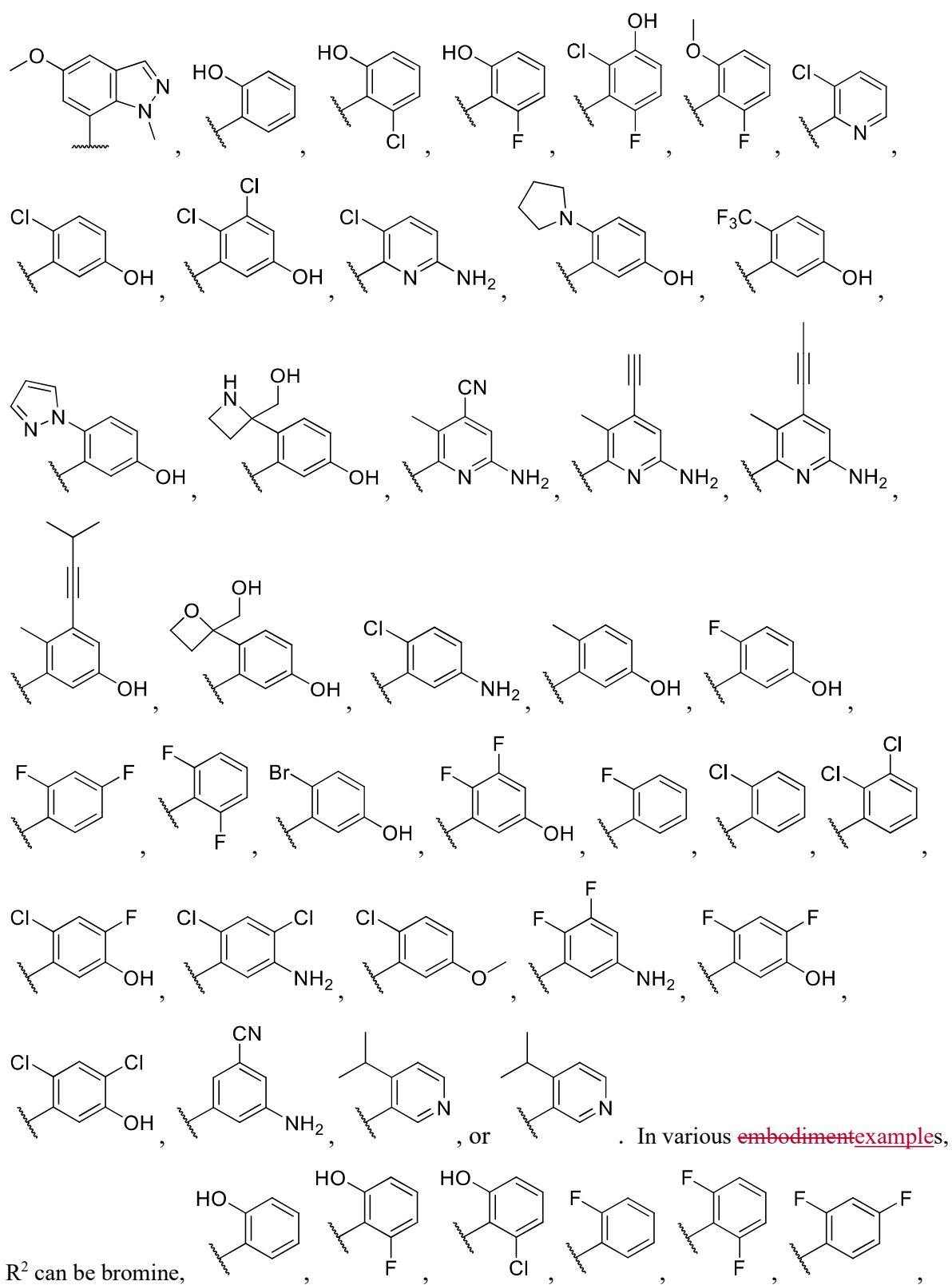
[0019] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some **embodimentexamples**, each of E^1 and E^2 is CR^1 . In other **embodimentexamples**, E^1 is CR^1 and E^2 is N. In some **embodimentexamples**, E^1 is N and E^2 is CR^1 . In various **embodimentexamples**, each of E^1 and E^2 is N.

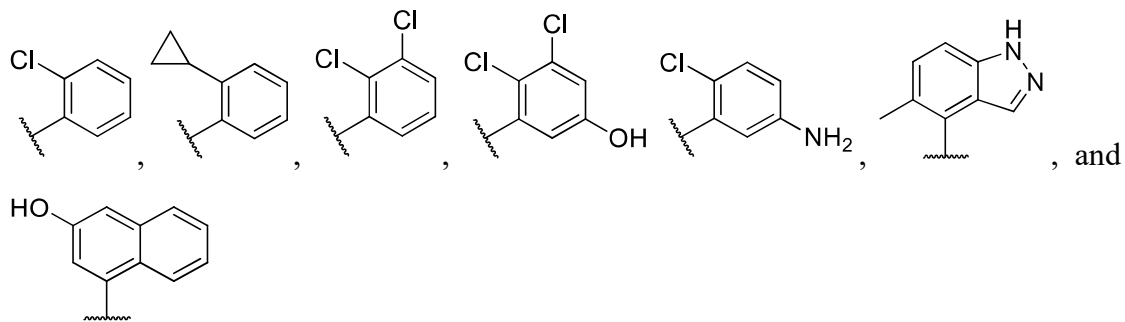
[0020] The compounds of formula (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In various **embodimentexamples**, R^{10} is C_{1-6} alkyl, aryl, heteroaryl, C_{3-14} cycloalkyl, C_{2-14} heterocycloalkyl, C_{1-6} alkoxy, O- C_{0-6} alkylene- 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 **embodimentexamples**, R^{10} is C_{1-8} alkyl. In some **embodimentexamples**, R^{10} is C_{0-3} alkylene- C_{6-14} aryl. In some **embodimentexamples**, R^{10} is C_{0-3} alkylene- C_{2-14} heteroaryl. In some **embodimentexamples**, R^{10} is C_{0-3} alkylene- C_{3-14} cycloalkyl. In some **embodimentexamples**, R^{10} is C_{0-3} alkylene- C_{2-14} heterocycloalkyl. In other **embodimentexamples**, R^{10} is C_{0-6} alkyleneamine. For example, R^{10} can be *i*-Pr, *t*-Bu, phenyl, benzyl, OCH₃, Cl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,











[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 various **embodimentexamples**, R^3 is halo. In various **embodimentexamples**, R^3 is Cl. In some **embodimentexamples**, R^3 is C_{1-2} alkyl. In some **embodimentexamples**, R^3 is methyl. In some **embodimentexamples**, R^3 is C_{1-2} haloalkyl. In various **embodimentexamples**, R^3 is CF_3 .

[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 some **embodimentexamples**, R^4 is



some **embodimentexamples**, R^4 is

In some **embodimentexamples**, R^4

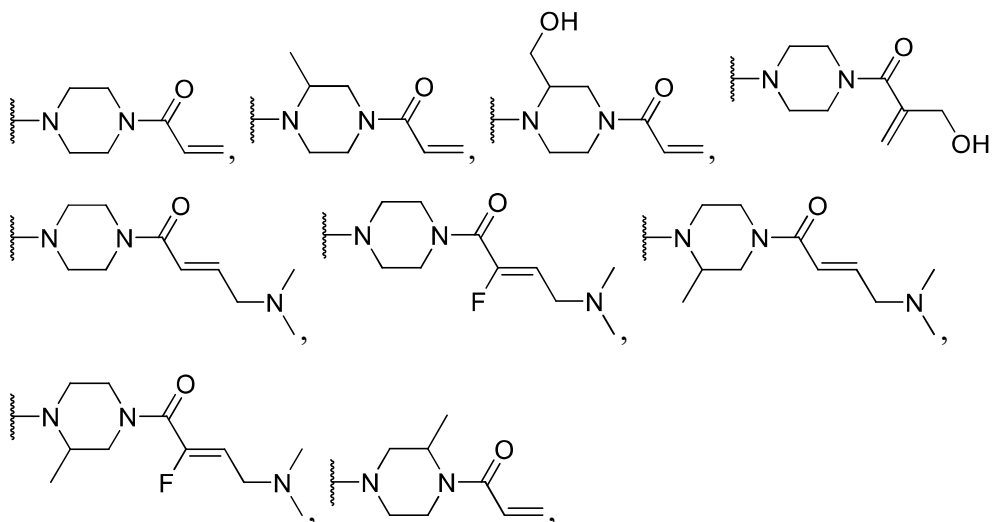
is

In some **embodimentexamples**, R^4 is

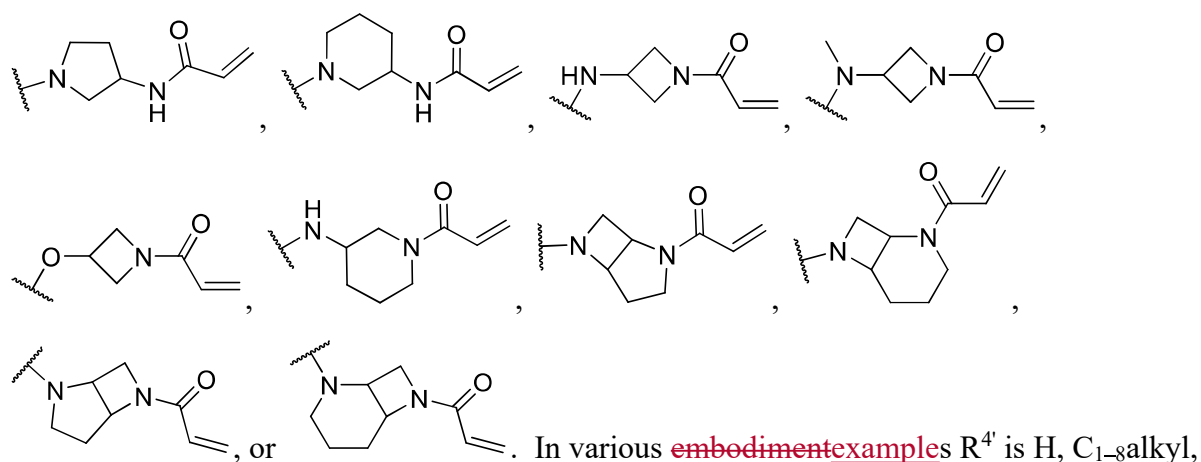
In some

embodimentexamples, R^4 is

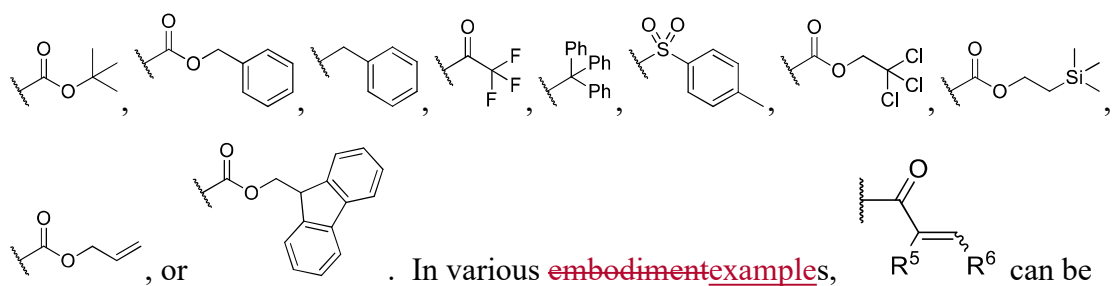
In some **embodimentexamples**, R^4 can be



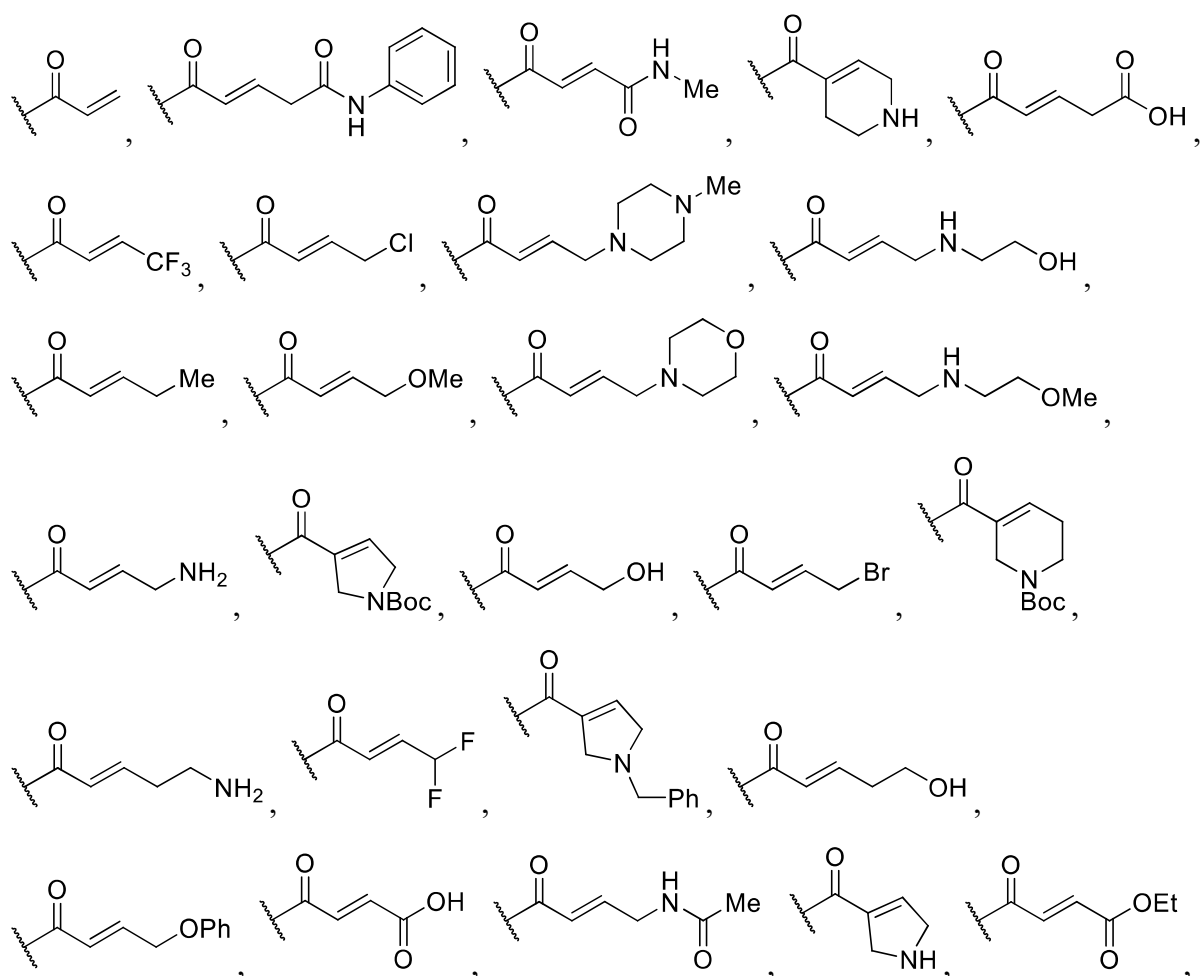




In various **embodimentexamples** R^4 is H, C_{1-8} alkyl, C_{2-8} alkynyl, C_{1-6} alkylene-O- C_{1-4} alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, C_{0-3} alkylene- C_{3-8} cycloalkyl, C_{0-3} alkylene- C_{2-7} heterocycloalkyl, C_{0-3} alkylene- C_{6-14} aryl, or selected from

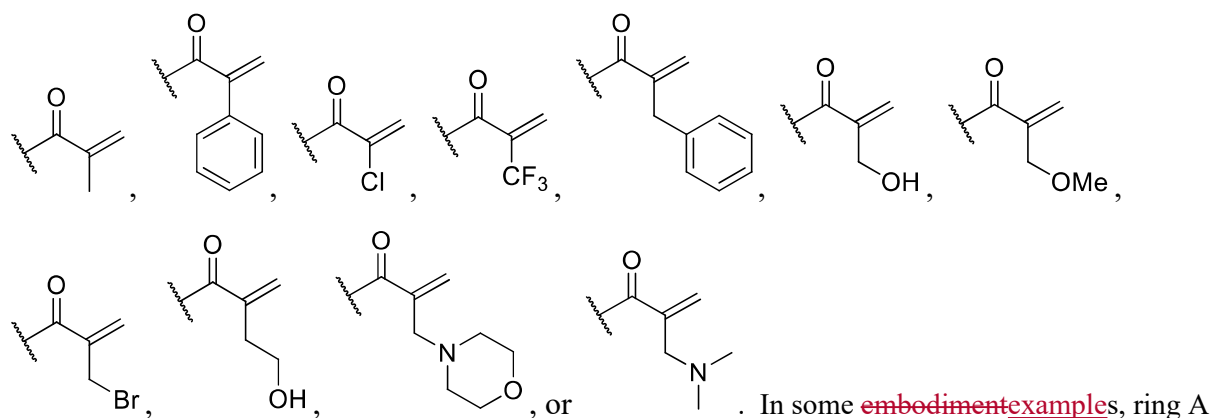


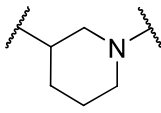
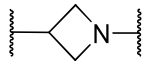
In various **embodimentexamples**, R^5 R^6 can be

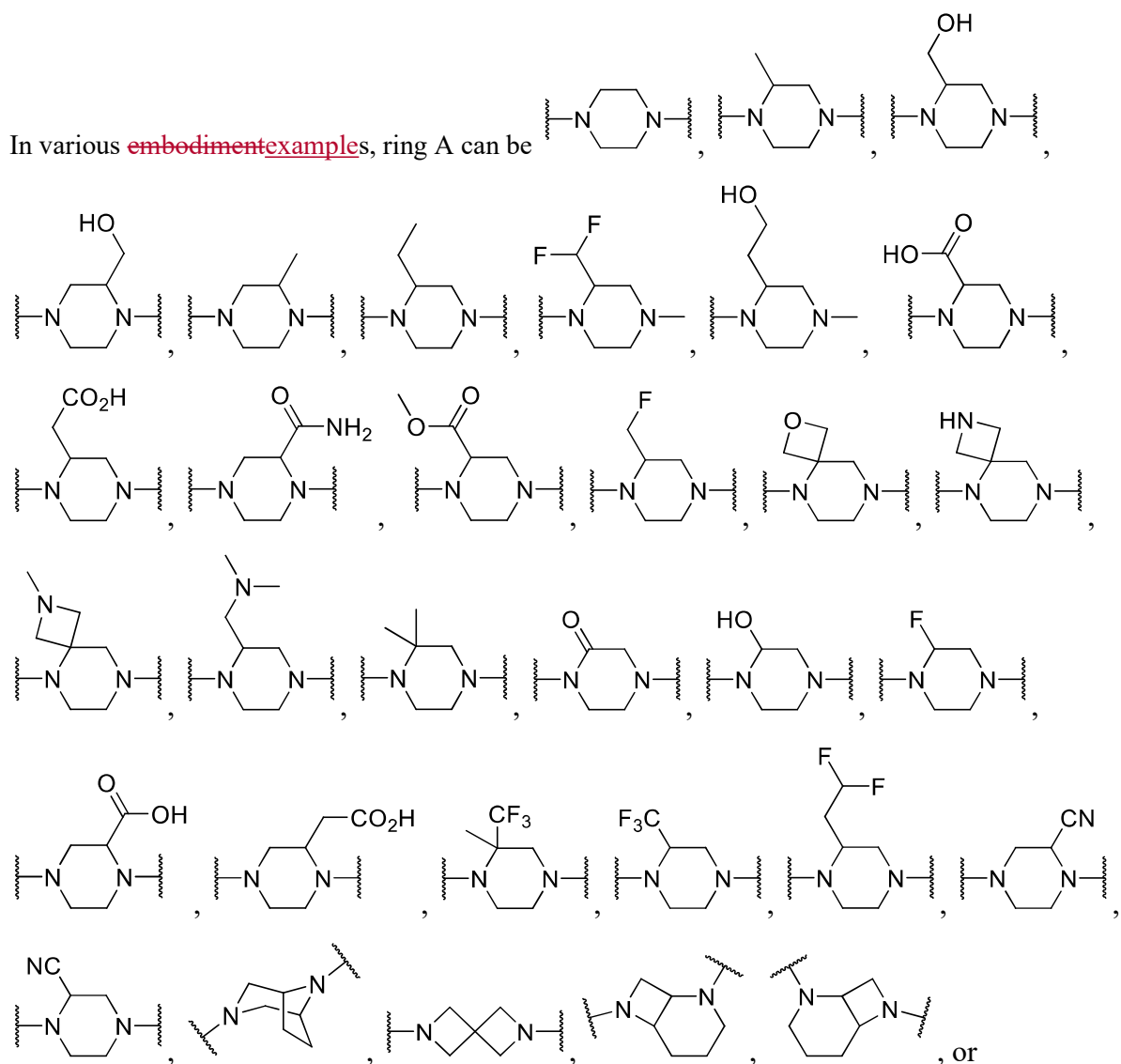


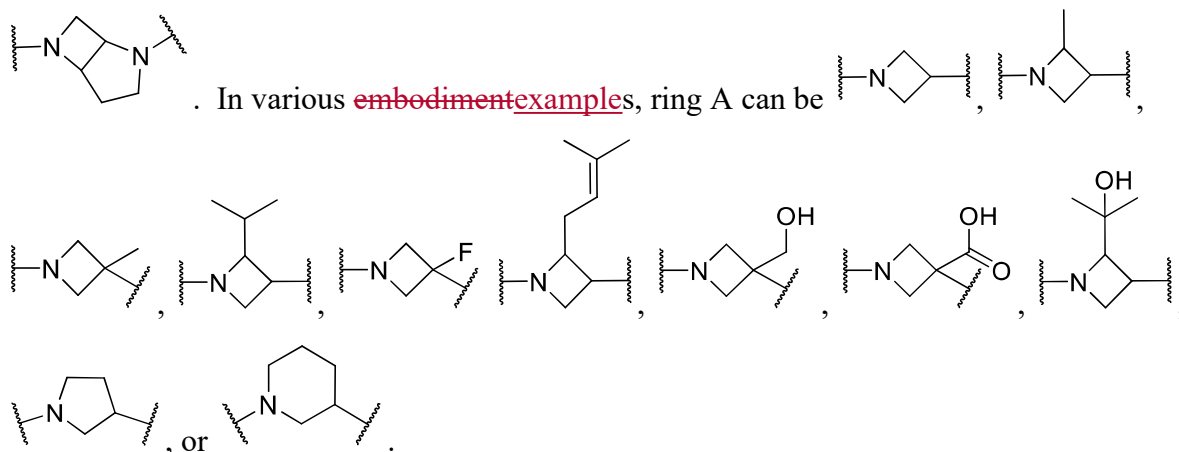






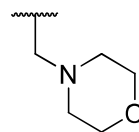
is  or  . In some **embodimentexamples**, ring A comprises piperidinyl, piperazinyl, pyrrolidinyl, or azetidyl. In some **embodimentexamples**, ring A comprises piperidinyl.



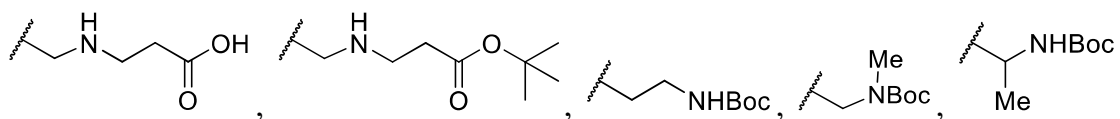


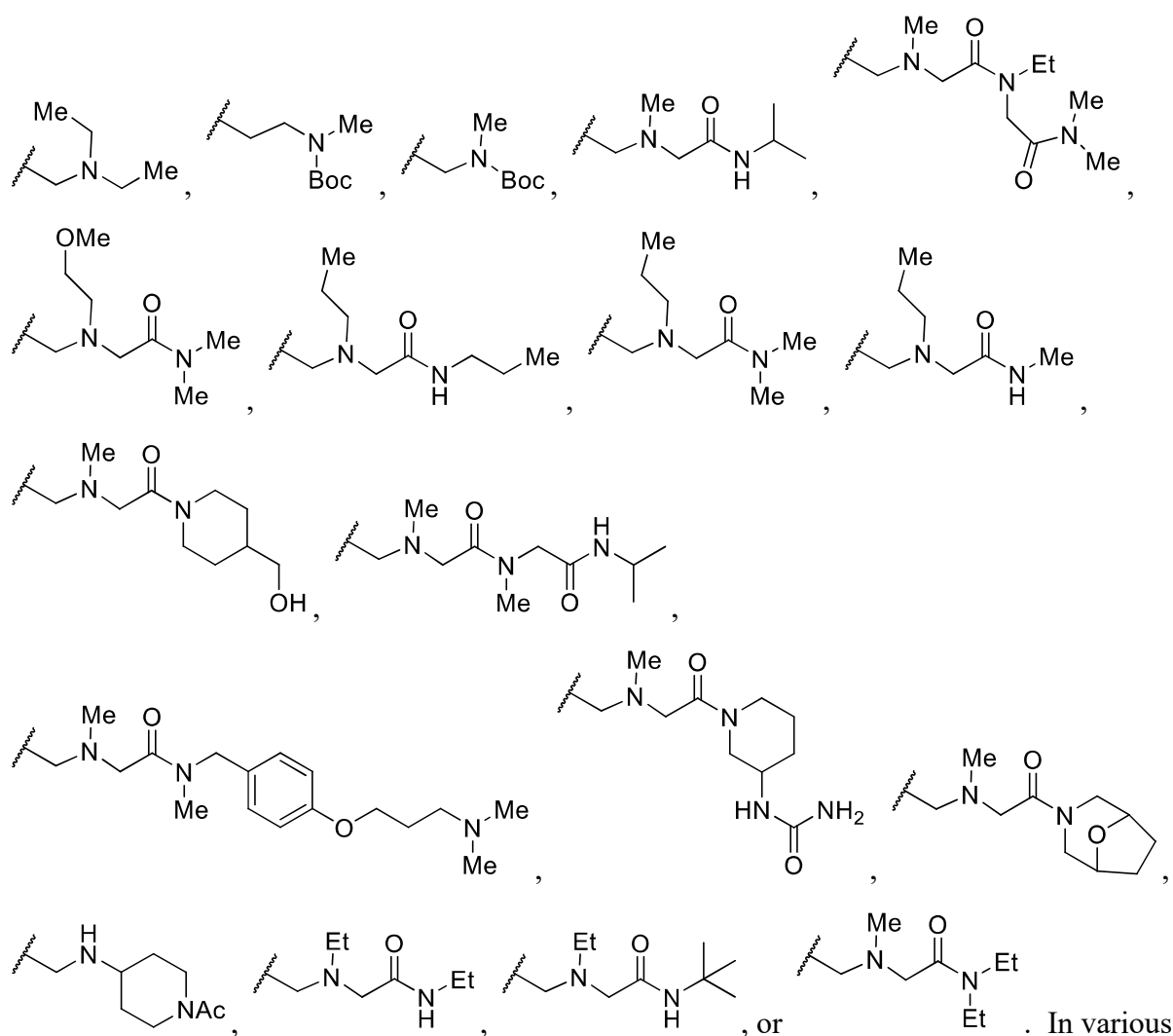
[0025] The compounds of formula (I), (II), (III), (III'), (IV), (IV'), or (V) as disclosed herein can have one or more of the following features. In some **embodimentexamples**, L is a bond. In some **embodimentexamples**, L is C₁₋₂alkylene. In various **embodimentexamples**, L is O. In some **embodimentexamples**, L is S. In various **embodimentexamples**, L is NH. In some **embodimentexamples**, R⁵ is H or halo. In some **embodimentexamples**, R⁵ is H, Br, Cl, F, CN, CH₃, CF₃, CH₂Br, CH₂OH, CH₂CH₂OH, CH₂OCH₂phenyl, cyclopropyl, phenyl, CH₂phenyl, CH₂OCH₃, CH₂N(CH₃)₂, CH₂N(CH₂CH₃)₂, CH₂CO₂H, CH₂CO₂CH₃,

CH₂NHC(O)CH₃, CH₂C(O)NHCH₃, CH₂OC(O)CH₃, or

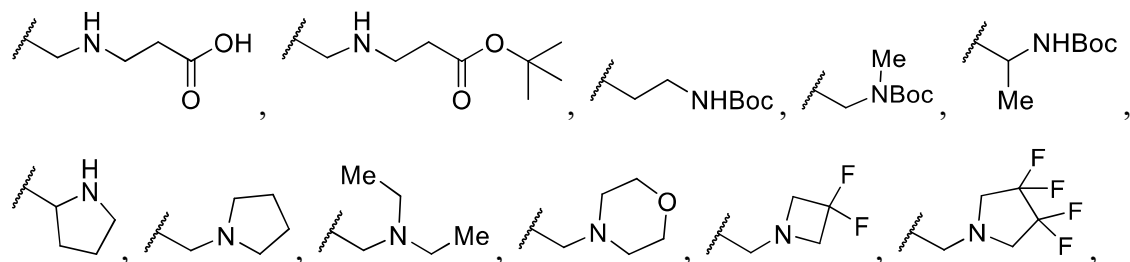


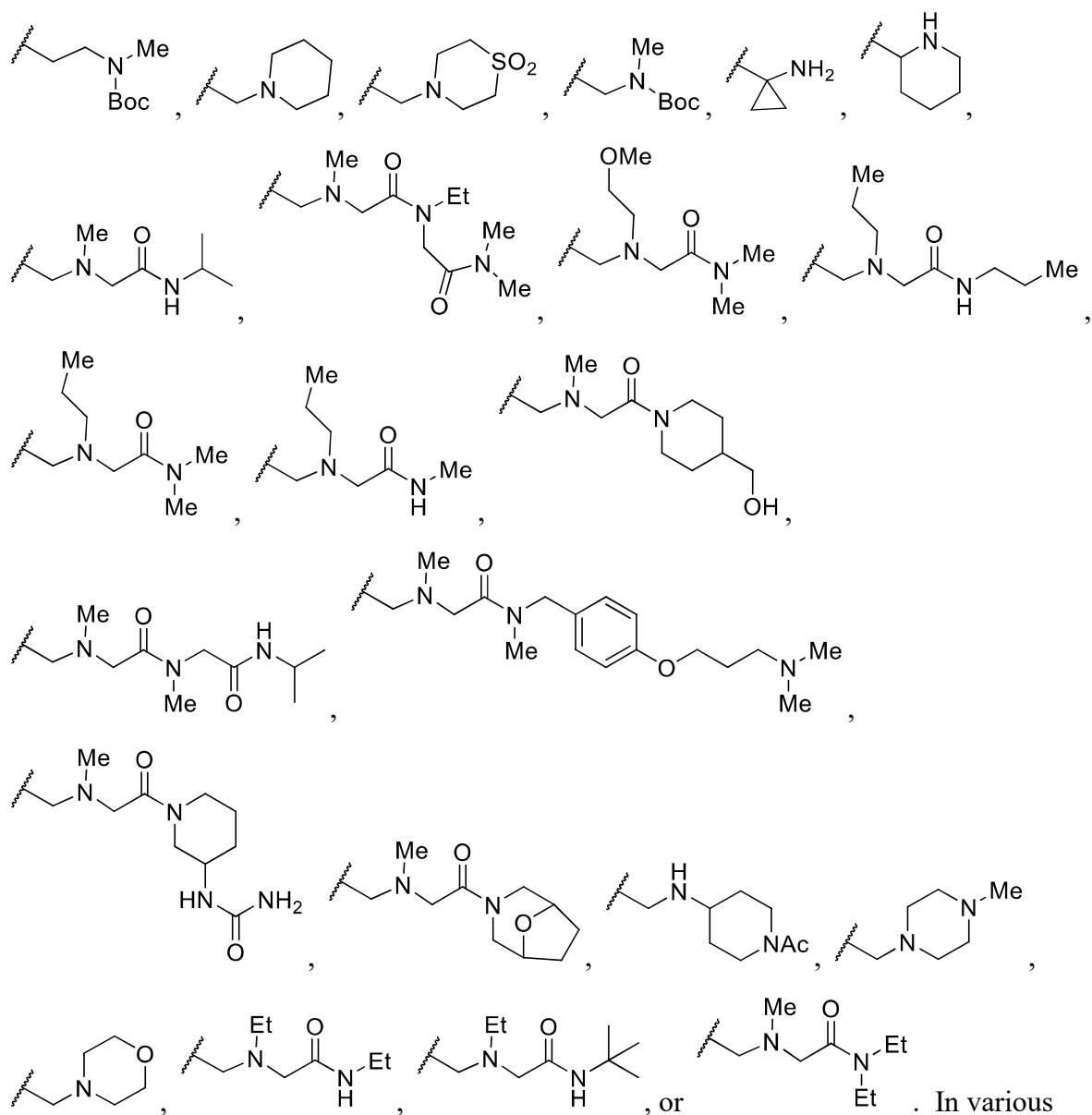
. In some **embodimentexamples**, R⁶ is C₁₋₆alkyl, C₁₋₆alkylene-O-C₁₋₆alkyl, C₁₋₆alkylene-OH, C₁₋₃haloalkyl, C₁₋₆alkylene-amine, C₀₋₆alkylene-amide, C₀₋₁alkylene C(O)OC₁₋₃alkyl, C₀₋₁alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₁alkylene-C₃₋₁₄cycloalkyl, or C₀₋₃alkylene-C₆₋₁₄aryl. In various **embodimentexamples**, R⁶ is C₀₋₆alkylene-amine or C₀₋₃alkylene-amide and is CH₂NH₂, CH(CH₃)NH₂, CH(CH₃)₂NH₂, CH₂CH₂NH₂, CH₂CH₂N(CH₃)₂, CH₂NHCH₃, C(O)NHCH₃, C(O)N(CH₃)₂, CH₂C(O)NHphenyl, CH₂NHC(O)CH₃, CH₂NHCH₂CH₂OH, CH₂NHCH₂CO₂H, CH₂NH(CH₃)CH₂CO₂CH₃, CH₂NHCH₂CH₂OCH₃, CH₂NH(CH₃)CH₂CH₂OCH₃, CH₂NH(CH₃)CH₂C(O)N(CH₃)₂, CH₂NH(CH₃)CH₂C(O)NHCH₃, CH₂NMe₂, CH₂NH(CH₃)CH₂CH₂OH, CH₂NH(CH₃)CH₂CH₂F, CH₂N⁺(CH₃)₃, CH₂NHCH₂CHF₂, CH₂NHCH₂CH₃,



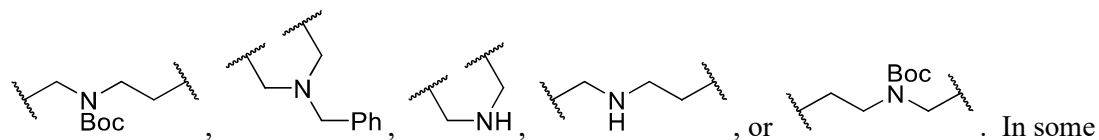


embodiment examples, R^6 is phenyl, cyclopropyl, CH_3 , CF_3 , CH_2CH_3 , CH_2NH_2 , $CH(CH_3)NH_2$, $CH(CH_3)_2NH_2$, CH_2Cl , CH_2Br , CH_2OCH_3 , $CH_2Ophenyl$, CH_2OH , CO_2H , $CO_2CH_2CH_3$, CH_2CO_2H , $CH_2CH_2NH_2$, CH_2CH_2OH , $CH_2CH_2N(CH_3)_2$, CH_2NHCH_3 , $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $CH_2C(O)NHphenyl$, 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 , $CH_2NH(CH_3)CH_2CH_2OH$, $CH_2NH(CH_3)CH_2CH_2F$, $CH_2N^+(CH_3)_3$, $CH_2NHCH_2CHF_2$, $CH_2NHCH_2CH_3$,





embodiment examples, R^5 and R^6 together are . In various



embodiment examples, each of R^5 and R^6 is H. In some **embodiment examples**, R^7 is H. In some **embodiment examples**, R^7 is methyl. In various **embodiment examples**, R^7 and R^5 together are $-\text{CH}_2-$ or $-\text{C}(\text{O})\text{CH}_2-$.

[0026] 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.

[0027] 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 **embodimentexamples**, the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

DETAILED DESCRIPTION

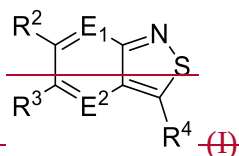
Definitions

Abbreviations: The following abbreviations may be used herein:

AcOH	acetic acid
aq or aq.	Aqueous
BOC or Boc	tert-butyloxycarbonyl
cpme	cyclopentyl methyl ether
DCE	1,2-dichloroethane
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DMA	N,N-Dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Dppf, DPPF or dppf	1,1'-bis(diphenylphosphino)ferrocene
eq or eq. or equiv.	Equivalent
ESI or ES	electrospray ionization
Et	Ethyl
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
g	Grams
h	Hour
HPLC	high pressure liquid chromatography
iPr	Isopropyl
iPr ₂ NEt or DIPEA	N-ethyl diisopropylamine (Hünig's base)
KHMDS	potassium hexamethyldisilazide
KOAc	potassium acetate
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane, 2,4-Bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide
LC MS, LCMS, LC-MS or LC/MS	liquid chromatography mass spectroscopy
LG	Leaving group (e.g., halogen, mesylate, triflate)
LHMDS or LiHMDS	lithium hexamethyldisilazide
m/z	mass divided by charge
Me	Methyl

What is Claimed:

1. ~~A compound having a structure of formula (I)~~



~~wherein~~

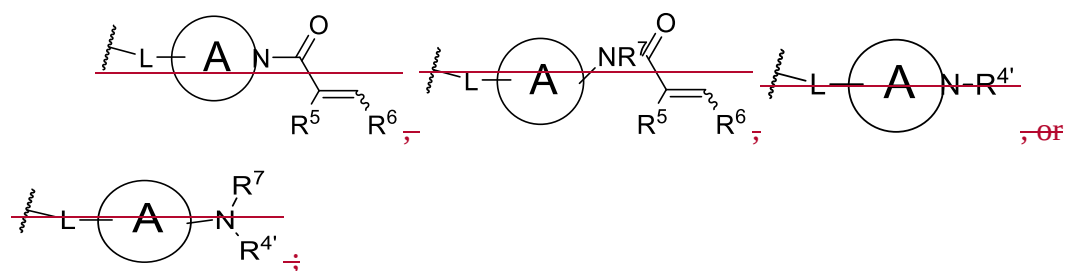
~~E¹ and E² are each independently N or CR¹;~~

~~R¹ is independently H, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, NH-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, cyano, or halo;~~

~~R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7 membered ring;~~

~~R³ is halo, C₁₋₃alkyl, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₄cycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;~~

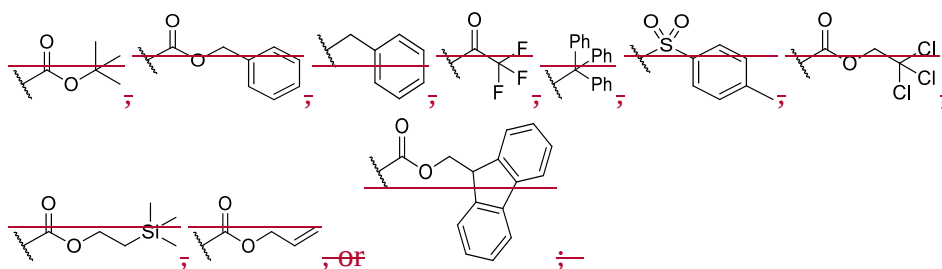
~~R⁴ is~~



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

~~L is a bond, C₁₋₆alkylene, O-C₀₋₅alkylene, S-C₀₋₅alkylene, or NH-C₀₋₅alkylene, and for C₂₋₆alkylene, O-C₂₋₅alkylene, S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;~~

~~R^{4'} is H, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, cycloalkyl, heterocycloalkyl, C₀₋₃alkylene-C₃₋₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or selected from~~

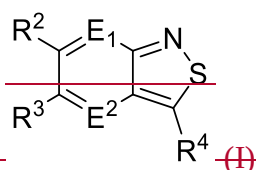


R^5 and R^6 are each independently H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} alkylene-O- C_{1-4} alkyl, C_{1-6} alkylene-OH, C_{1-6} haloalkyl, C_{1-6} alkyleneamine, C_{0-6} alkylene-amide, C_{0-3} alkylene-C(O)OH, C_{0-3} alkylene-C(O)OC $_{1-4}$ alkyl, C_{1-6} alkylene-O-aryl, C_{0-3} alkylene-C(O)C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

2. A compound having a structure of formula (I)



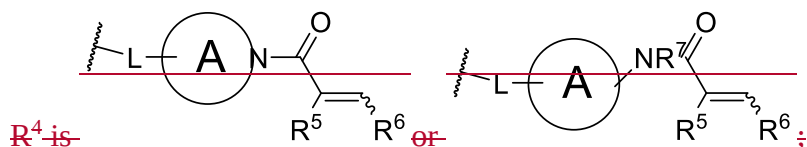
wherein

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;



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

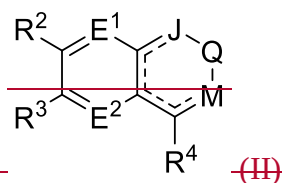
~~L is a bond, C_{1–6}alkylene, O–C_{0–5}alkylene, S–C_{0–5}alkylene, or NH–C_{0–5}alkylene, and for C_{2–6}alkylene, O–C_{2–5}alkylene, S–C_{2–5}alkylene, and NH–C_{2–5}alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;~~

~~R⁵ and R⁶ 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 R⁵ and R⁶, together with the atoms to which they are attached, form a 4–6 membered ring; and~~

~~R⁷ is H or C_{1–6}alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4–6 membered ring; or~~

~~a pharmaceutically acceptable salt thereof.~~

3. ~~A compound having a structure of formula (II)~~



~~wherein~~

~~E¹ and E² are each independently N or CR¹;~~

~~J is N, NR¹⁰, or CR¹⁰;~~

~~M is N, NR¹³, or CR¹³;~~

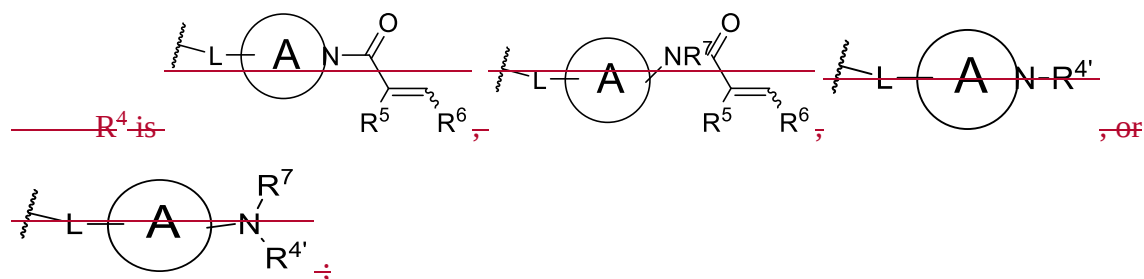
~~= is a single or double bond as necessary to give every atom its normal valence;~~

~~R¹ 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;~~

~~R² 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–}~~

~~C₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R² substituents, together with the nitrogen atom to which they are attached, form a 3-7 membered ring;~~

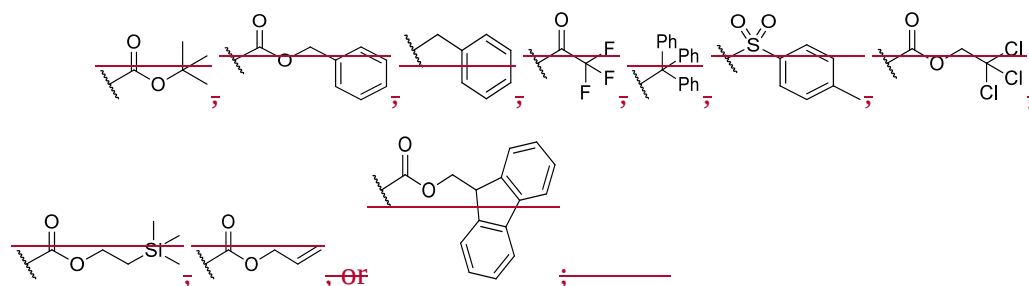
~~R³ is halo, C₁₋₃alkyl, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;~~



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

~~L is a bond, C₁₋₆alkylene, O-C₀₋₅alkylene, S-C₀₋₅alkylene, or NH-C₀₋₅alkylene, and for C₂₋₆alkylene, O-C₂₋₅alkylene, S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;~~

~~R⁴ is H, C₁₋₈alkyl, C₂₋₈alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, cycloalkyl, heterocycloalkyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or selected from~~



~~R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring;~~

~~R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached,~~

form a 4-6 membered ring;

~~Q is CR⁸R⁹, C=CR⁸R⁹, C=O, C=S, or C=NR⁸;~~

~~R⁸ and R⁹ are each independently H, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, cyano, nitro, or C₃₋₆cycloalkyl, or R⁸ and R⁹, taken together with the carbon atom to which they are attached, can form a 3-6 membered ring;~~

~~R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; and~~

~~R¹³ is C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, or C₃₋₁₄cycloalkyl; or~~

~~a pharmaceutically acceptable salt thereof;~~

~~with the proviso that~~

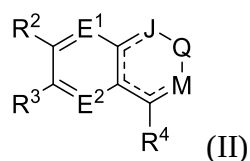
~~(1) when J is NR¹⁰, M is N or CR¹³;~~

~~(2) when M is NR¹³, J is N or CR¹⁰;~~

~~(3) when J is CR¹⁰, M is N or NR¹³; and~~

~~(4) when M is CR¹³, J is N or NR¹⁰.~~

41. A compound having a structure of formula (II)



wherein

E¹ and E² are each independently N or CR¹;

J is N, NR¹⁰, or CR¹⁰;

M is N, NR¹³, or CR¹³;

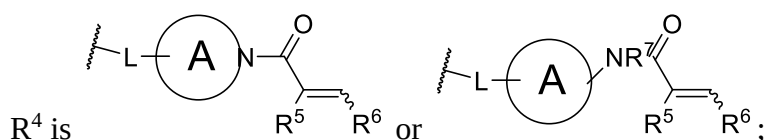
== is a single or double bond as necessary to give every atom its normal valence;

R¹ is independently H, hydroxy, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, NH-C₁₋₄alkyl, N(C₁₋₄alkyl)₂, cyano, or halo;

R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋

6alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₃₋₁₄heterocycloalkyl, ~~C₂₋₁₄heterocycloalkyl~~, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R³ is halo, C₁₋₃alkyl, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₄cycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;



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

L is a bond, C₁₋₆alkylene, -O-C₀₋₅alkylene, -S-C₀₋₅alkylene, or -NH-C₀₋₅alkylene, and for C₂₋₆alkylene, -O-C₂₋₅alkylene, -S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4–6 membered ring;

R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4–6 membered ring;

Q is CR⁸R⁹, C=CR⁸R⁹, C=O, C=S, or C=NR⁸;

R⁸ and R⁹ are each independently H, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, cyano, nitro, or C₃₋₆cycloalkyl, or R⁸ and R⁹, taken together with the carbon atom to which they are attached, can form a 3–6 membered ring;

R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; and

R¹³ is C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, or C₃₋₁₄cycloalkyl; 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} ;

wherein

an alkyl, alkylene, alkenyl, alkynyl or alkoxy group is optionally substituted with one or more groups independently selected from halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, -NC, amino, - CO_2H , - $\text{CO}_2\text{C}_{1-8}$ alkyl, - OCOC_{1-8} alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ heterocycloalkyl, $\text{C}_5\text{-C}_{10}$ aryl, and $\text{C}_5\text{-C}_{10}$ heteroaryl;

an aryl group is unsubstituted or optionally substituted with one or more groups independently selected from halo, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, - CF_3 , - OCF_3 , - NO_2 , -CN, -NC, -OH, alkoxy, - CO_2H , - $\text{CO}_2\text{C}_{1-8}$ alkyl, - OCOC_{1-8} alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ heterocycloalkyl, $\text{C}_5\text{-C}_{10}$ aryl, and $\text{C}_5\text{-C}_{10}$ heteroaryl;

a cycloalkyl or heterocycloalkyl group is unsubstituted or optionally substituted with one or more groups selected from halo, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, - OCF_3 , - NO_2 , -CN, -NC, -OH, alkoxy, amino, - CO_2H , - $\text{CO}_2\text{C}_{1-8}$ alkyl, - OCOC_{1-8} alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ heterocycloalkyl, $\text{C}_5\text{-C}_{10}$ aryl, and $\text{C}_5\text{-C}_{10}$ heteroaryl; and

a heteroaryl group is unsubstituted or optionally substituted with one or more substituents selected from halo, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, - OCF_3 , - NO_2 , -CN, -NC, -OH, alkoxy, amino, - CO_2H , - $\text{CO}_2\text{C}_{1-8}$ alkyl, - OCOC_{1-8} alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ heterocycloalkyl, $\text{C}_5\text{-C}_{10}$ aryl, and $\text{C}_5\text{-C}_{10}$ heteroaryl.

~~5. The compound of claim 3 or 4, wherein when Q is C=O; and E^1 and E^2 are each CR^1 ; then either~~

~~—— (1) R^{10} is C_{1-3} alkylene- C_{6-14} aryl, C_{1-3} alkylene- C_{3-14} heteroaryl, 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.~~

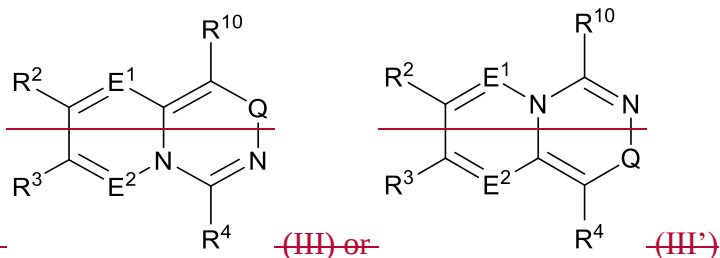
~~6. The compound of claim 3 or 4, wherein J is NR^{10} and M is CR^{13} .~~

~~7. The compound of claim 3 or 4, wherein J is CR^{10} and M is NR^{13} .~~

~~8. The compound of claim 3 or 4, wherein J is N and M is NR^{13} .~~

29. The compound of claim ~~3~~ or ~~41~~, wherein J is NR¹⁰ and M is N.

~~9-10. A compound having a structure of formula (III) or (III'):~~



wherein

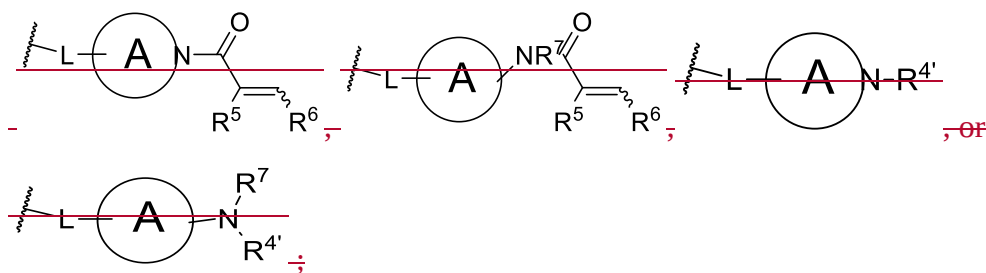
~~—E¹ and E² are each independently N or CR¹;~~

~~—R¹ is independently H, hydroxy, C₁₋₆alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, NH-C₁₋₄alkyl, N(C₁₋₄alkyl)₂, cyano, or halo;~~

~~—R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7 membered ring;~~

~~—R³ is halo, C₁₋₃alkyl, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;~~

~~—R⁴ is~~

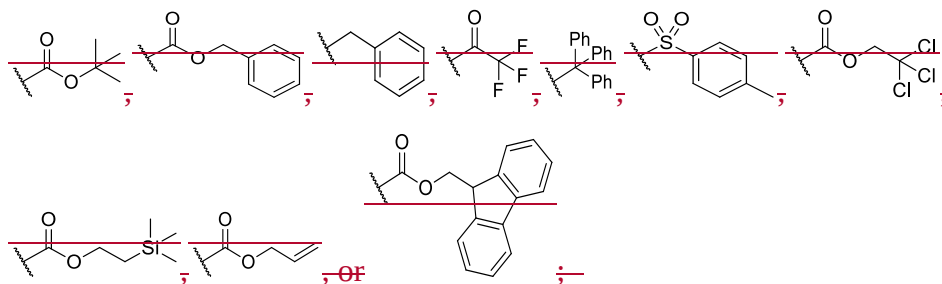


~~ring A is a monocyclic 4-7 membered ring or a bicyclic, bridged, fused, or spiro 6-11 membered ring;~~

~~—L is a bond, C₁₋₆alkylene, O-C₀₋₅alkylene, S-C₀₋₅alkylene, or NH-C₀₋₅alkylene, and for C₂₋₆alkylene, O-C₂₋₅alkylene, S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;~~

~~—R^{4'} is H, C₁₋₈alkyl, C₂₋₈alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆~~

~~haloalkyl, cycloalkyl, heterocycloalkyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or selected from~~



~~R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring;~~

~~— R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4-6 membered ring;~~

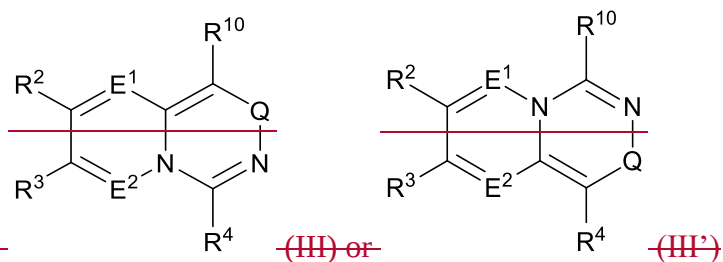
~~— Q is CR⁸R⁹, C=CR⁸R⁹, C=O, C=S, or C=NR⁸;~~

~~— R⁸ and R⁹ are each independently H, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, cyano, nitro, or C₃₋₁₄cycloalkyl, or R⁸ and R⁹, taken together with the carbon atom to which they are attached, can form a 3-6 membered ring;~~

~~— R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or~~

~~a pharmaceutically acceptable salt thereof.~~

11. — A compound having a structure of formula (III) or (III'):



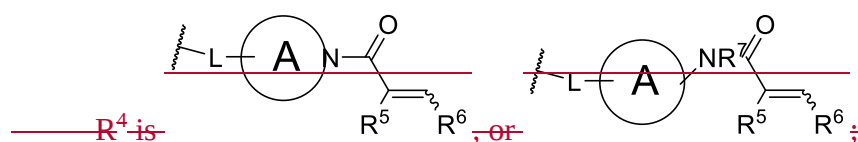
wherein

— 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;



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

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

a pharmaceutically acceptable salt thereof.

12. The compound of claim 10 or 11, having a structure of formula (III).

13. The compound of claim 10 or 11, having a structure of formula (III').

14. The compound of any one of claims 3 to 12, wherein Q is $\text{C}=\text{O}$.

15. The compound of any one of claims 3 to 12, wherein Q is $\text{C}=\text{S}$.

16. The compound of any one of claims 3 to 12, wherein Q is $\text{C}=\text{NR}^8$.

17. The compound of claim 16, wherein R^8 is C_{1-2} alkyl.

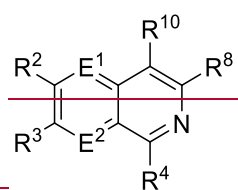
18. The compound of any one of claims 3 to 12, wherein Q is CR^8R^9 .

19. The compound of any one of claims 3 to 12, wherein Q is $\text{C}=\text{CR}^8\text{R}^9$.

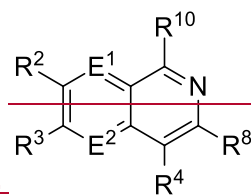
20. The compound of claim 18 or 19, wherein R^8 and R^9 , taken together with the carbon atom to which they are attached, form a 3-4 membered ring.

21. The compound of claim 18 or 19, wherein R^8 is C_{1-2} alkyl, and R^9 is H.

22. A compound having a structure of formula (IV) or (IV'):



(IV) or



(IV')

wherein

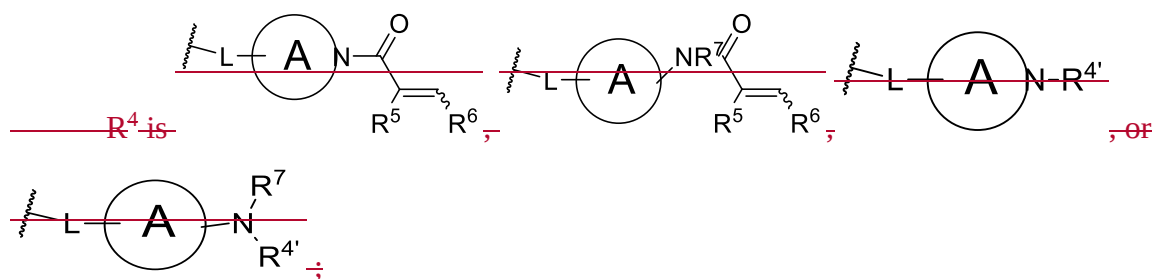
— E^1 and E^2 are each independently CR^1 or N;

— R^1 is independently H, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $\text{NH}-\text{C}_{1-6}$ alkyl,

~~N(C₁₋₆alkyl)₂, cyano, or halo;~~

~~— R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7 membered ring;~~

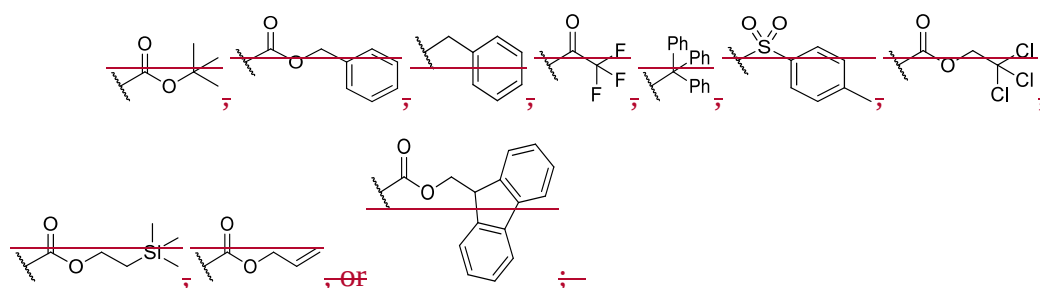
~~— R³ is halo, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₄cycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;~~



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

~~— L is a bond, C₁₋₆alkylene, O-C₀₋₅alkylene, S-C₀₋₅alkylene, or NH-C₀₋₅alkylene, and for C₂₋₆alkylene, O-C₂₋₅alkylene, S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;~~

~~— R⁴ is H, C₁₋₈alkyl, C₂₋₈alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, cycloalkyl, heterocycloalkyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or selected from~~



~~R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋~~

~~alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring;~~

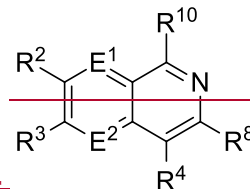
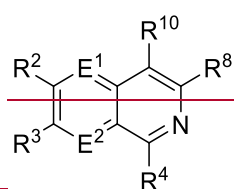
~~—— R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4-6 membered ring;~~

~~—— R⁸ is H, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, halo, cyano, nitro, C₃₋₁₄cycloalkyl, or NR¹¹R¹²;~~

~~—— R¹¹ and R¹² are each independently H, C₁₋₈alkyl, or C₃₋₁₄cycloalkyl; and~~

~~—— R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₂₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, N-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, N-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or a pharmaceutically acceptable salt thereof.~~

23. — A compound having a structure of formula (IV) or (IV'):



~~(IV) or~~

~~(IV')~~

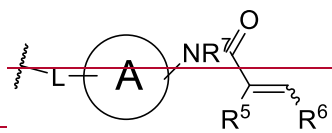
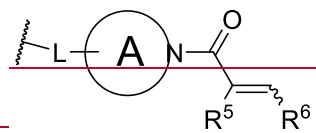
wherein

~~—— E¹ and E² are each independently CR¹ or N;~~

~~—— R¹ is independently H, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, NH-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, cyano, or halo;~~

~~—— R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached, form a 3-7 membered ring;~~

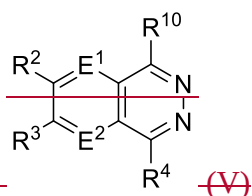
~~—— R³ is halo, C₁₋₂haloalkyl, C₁₋₃alkoxy, C₃₋₁₄cycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl;~~



~~—— R⁴ 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;
- R⁵ and R⁶ 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 R⁵ and R⁶, together with the atoms to which they are attached, form a 4–6 membered ring;
- R⁷ is H or C_{1–8}alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4–6 membered ring;
- R⁸ is H, C_{1–3}alkyl, hydroxy, C_{1–3}alkoxy, halo, cyano, nitro, C_{3–14}cycloalkyl, or NR¹¹R¹²;
- R¹¹ and R¹² are each independently H, C_{1–8}alkyl, or C_{3–15}cycloalkyl; and
- R¹⁰ 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.
24. — The compound of claim 22 or 23, having a structure of formula (IV).
25. — The compound of claim 22 or 23, having a structure of formula (IV').
26. — The compound of any one of claims 22 to 25, wherein E¹ and E² are each CR¹, and R⁸ is hydroxy, halo, nitro, or C_{3–6}cycloalkyl.
27. — The compound of any one of claims 22 to 25, wherein R⁸ is methyl.

28. — A compound having a structure of formula (V):



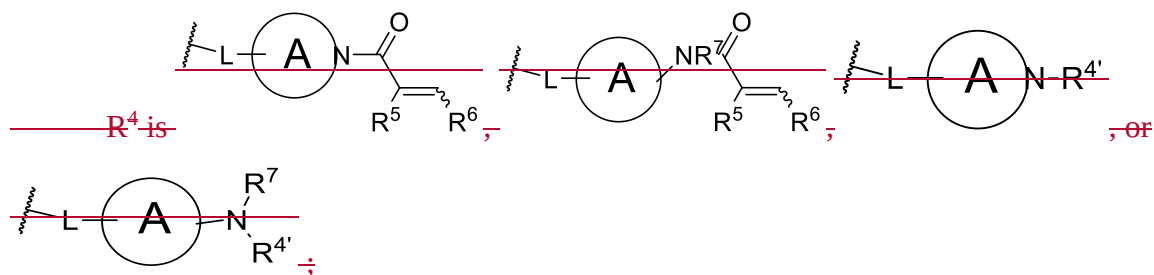
wherein

— 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;

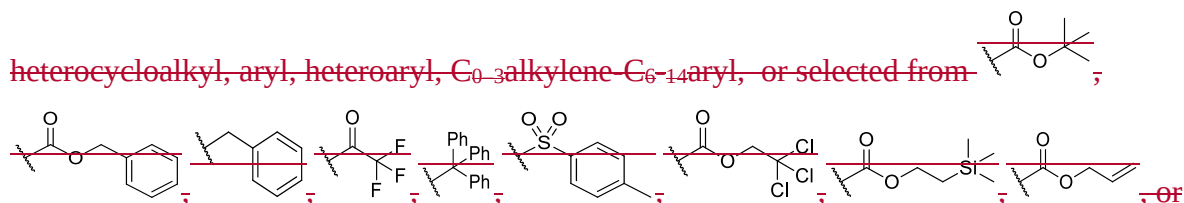
— R^3 is halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-14} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, or heteroaryl;

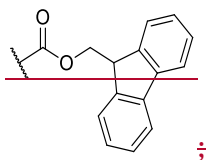


— ring A is a monocyclic 4-7 membered ring or a bicyclic, bridged, fused, or spiro 6-11 membered ring;

— 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, cycloalkyl, heterocycloalkyl, C_{0-3} alkylene- C_{3-14} cycloalkyl, C_{0-3} alkylene- C_{2-14}





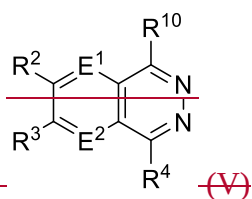
~~—R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring;~~

~~—R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4-6 membered ring; and~~

~~—R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or~~

~~a pharmaceutically acceptable salt thereof.~~

29. — A compound having a structure of formula (V):



wherein

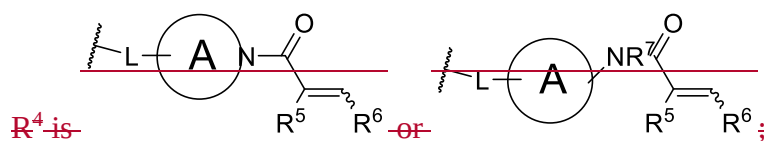
~~—E¹ and E² are each independently CR¹ or N;~~

~~—R¹ is independently H, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, NH-C₁₋₆alkyl, N(C₁₋₆alkyl)₂, cyano, or halo;~~

~~—R² is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, OR', N(R')₂, C₂₋₃alkenyl, C₂₋₃alkynyl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₆₋₁₄aryl, or C₀₋₃alkylene-C₂₋₁₄heteroaryl, and each R' is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₁₄cycloalkyl, C₂₋₁₄heterocycloalkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, aryl, or heteroaryl, or two R' substituents, together with the nitrogen atom to which they are attached,~~

form a 3-7 membered ring;

~~R³ is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₁₄cycloalkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, aryl, or heteroaryl;~~



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

~~L is a bond, C₁₋₆alkylene, O-C₀₋₅alkylene, S-C₀₋₅alkylene, or NH-C₀₋₅alkylene, and for C₂₋₆alkylene, O-C₂₋₅alkylene, S-C₂₋₅alkylene, and NH-C₂₋₅alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;~~

~~R⁵ and R⁶ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkylene-O-C₁₋₄alkyl, C₁₋₆alkylene-OH, C₁₋₆haloalkyl, C₁₋₆alkyleneamine, C₀₋₆alkylene-amide, C₀₋₃alkylene-C(O)OH, C₀₋₃alkylene-C(O)OC₁₋₄alkyl, C₁₋₆alkylene-O-aryl, C₀₋₃alkylene-C(O)C₁₋₄alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₂₋₁₄heteroaryl, or cyano, or R⁵ and R⁶, together with the atoms to which they are attached, form a 4-6 membered ring;~~

~~R⁷ is H or C₁₋₈alkyl, or R⁷ and R⁵, together with the atoms to which they are attached, form a 4-6 membered ring; and~~

~~R¹⁰ is C₁₋₈alkyl, C₀₋₃alkylene-C₆₋₁₄aryl, C₀₋₃alkylene-C₃₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, C₁₋₆alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₃₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₆₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, halo, cyano, or C₁₋₆alkylene-amine; or~~

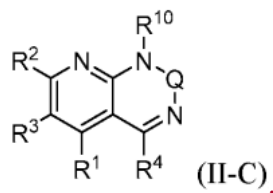
~~a pharmaceutically acceptable salt thereof.~~

~~30. The compound of any one of claims 1 to 29, wherein each of E¹ and E² is CR¹.~~

~~31. The compound of any one of claims 1, 2, 3, 4, 6 to 29 wherein E¹ is CR¹ and E² is N.~~

~~324. The compound of any one of claims 1, 2, 3, 4, 6 to 293, wherein E¹ is N and E² is CR¹.~~

5. The compound of any one of claims 1 to 4, wherein the compound is in the form of formula (II-C)



~~33. The compound of any one of claims 1, 2, 3, 4, 6 to 29, wherein each of E¹ and E² is N.~~

~~346. The compound of any one of claims 1, 2, 3, 4, 6 to 335, wherein R¹⁰ is C₁₋₆alkyl, aryl, heteroaryl or, C₃₋₁₄cycloalkyl, C₂₋₁₅heterocycloalkyl, C₁₋₄alkoxy, O-C₀₋₃alkylene-C₆₋₁₄aryl, O-C₀₋₃alkylene-C₂₋₁₄heteroaryl, O-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, O-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl, NH-C₁₋₈alkyl, N(C₁₋₈alkyl)₂, NH-C₀₋₃alkylene-C₃₋₁₄aryl, NH-C₀₋₃alkylene-C₂₋₁₄heteroaryl, NH-C₀₋₃alkylene-C₃₋₁₄cycloalkyl, or NH-C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl.~~

~~35. The compound of claim 28 or 29, wherein E¹ and E² are each CR¹, and R¹⁰ is C₁₋₃alkylene-C₆₋₁₄aryl, C₁₋₃alkylene-C₂₋₁₄heteroaryl, C₀₋₃alkylene-C₃₋₁₄cycloalkyl, C₁₋₃alkylene-C₂₋₁₄heterocycloalkyl, or halo.~~

~~36. The compound of any one of claims 3 to 33, wherein R¹⁰ is C₁₋₈alkyl.~~

~~37. The compound of any one of claims 3 to 33, wherein R¹⁰ is C₀₋₃alkylene-C₆₋₁₄aryl.~~

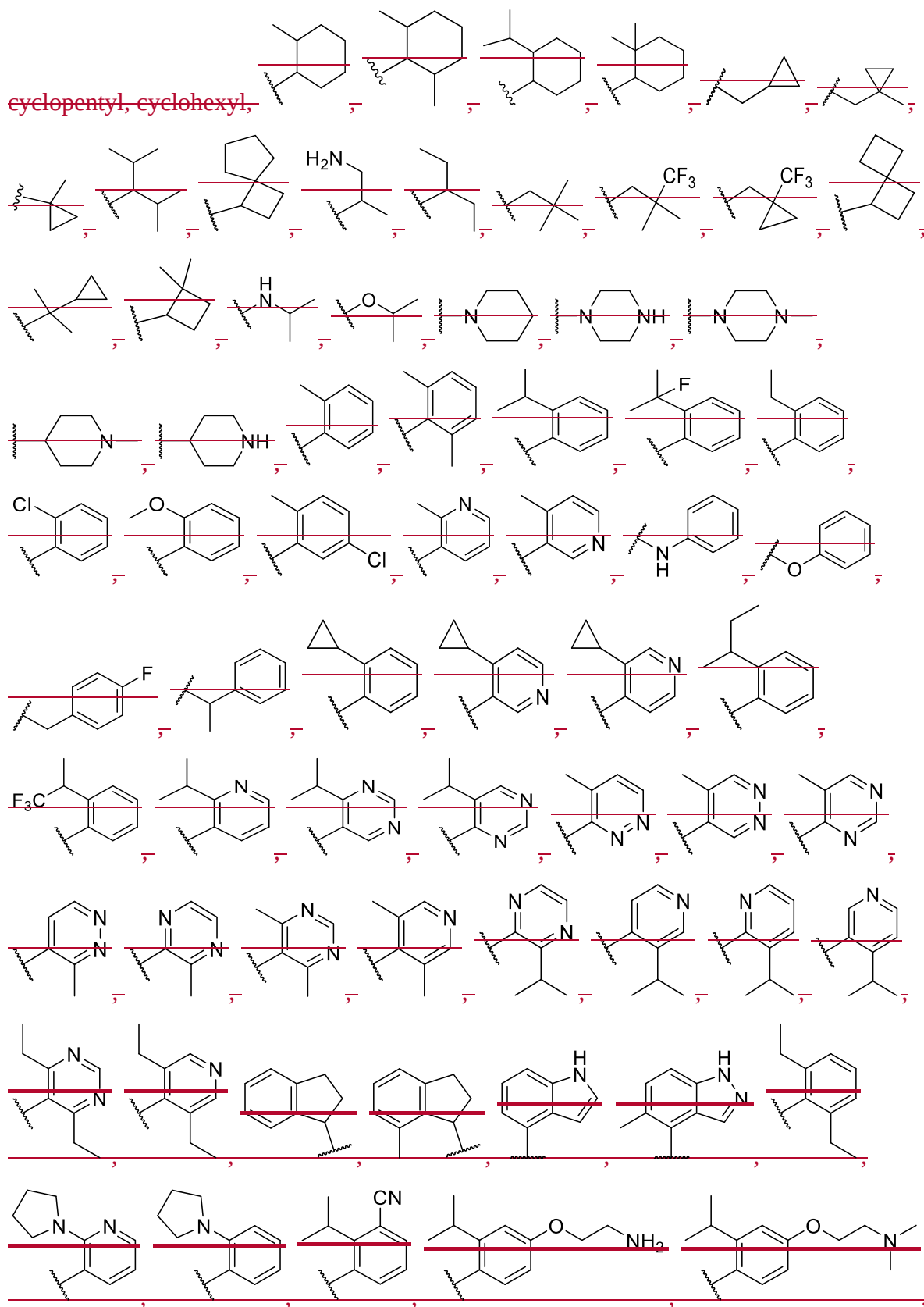
~~38. The compound of any one of claims 3 to 34, wherein R¹⁰ is C₀₋₃alkylene-C₃₋₁₄heteroaryl.~~

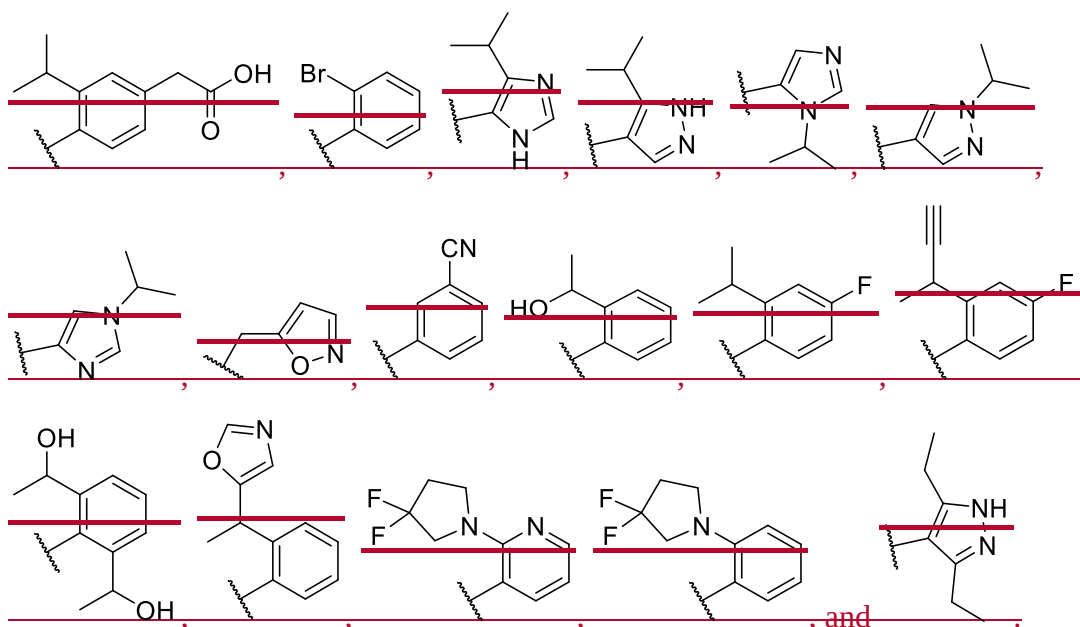
~~39. The compound of any one of claims 3 to 35, wherein R¹⁰ is C₀₋₃alkylene-C₃₋₁₄cycloalkyl.~~

~~40. The compound of any one of claims 3 to 24, 26, 27, and 30 to 33, wherein R¹⁰ is C₀₋₃alkylene-C₂₋₁₄heterocycloalkyl.~~

~~41. The compound of any one of claims 3 to 33, wherein R¹⁰ is C₀₋₆alkylene-amine.~~

42. — The compound of any one of claims 3 to 33, wherein R^{10} is selected from the group consisting of *i* Pr, *t* Bu, phenyl, benzyl, OCH_3 , Cl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

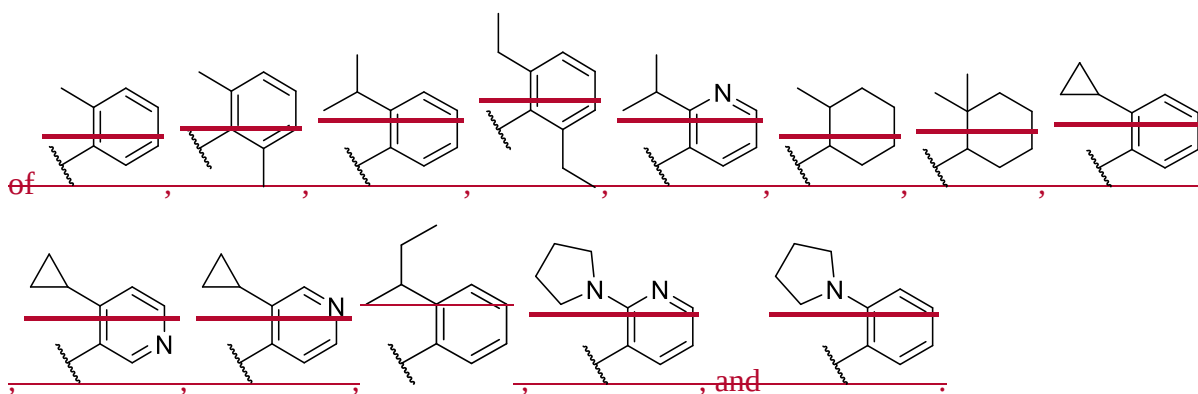




~~437.~~ The compound of any one of claims ~~3-1~~ to ~~336~~, wherein R^{10} comprises ~~ortho-substituted aryl~~, ortho-substituted heteroaryl, ~~or 2-substituted cyclohexyl~~.

~~8.~~ The compound of claim 7, wherein the heteroaryl comprises one or two ortho-substituents independently selected from the group consisting of methyl, ethyl, isopropyl and cyclopropyl.

~~44.~~ The compound of claim 43, wherein R^{10} is selected from the group consisting



~~459.~~ The compound of any one of claims 1 to ~~448~~, wherein R^1 is H.

~~46.~~ The compound of any one of claims 1 to 44, wherein R^1 is F.

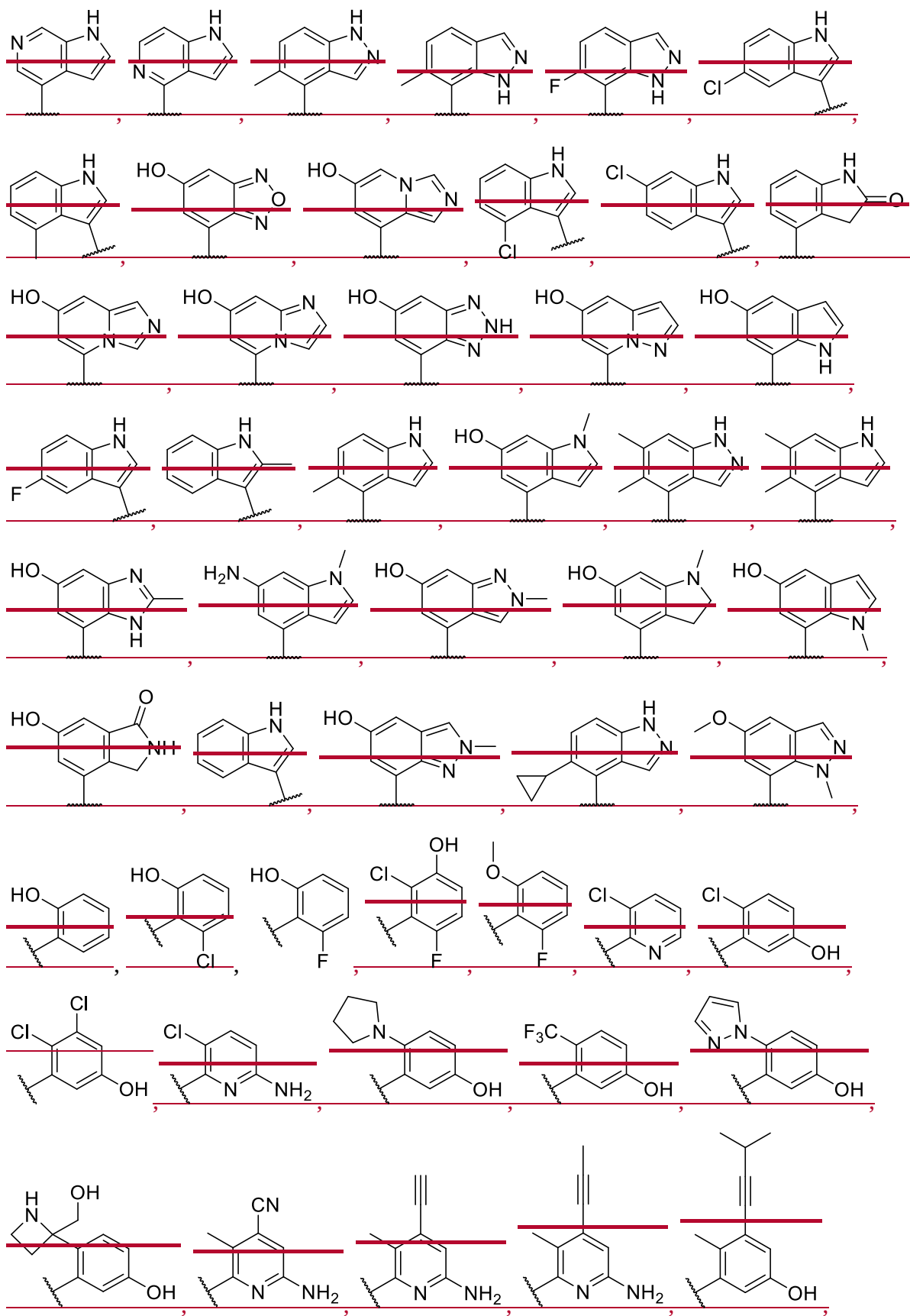
~~47.~~ The compound of any one of claims 1 to 44, wherein R^1 is methyl.

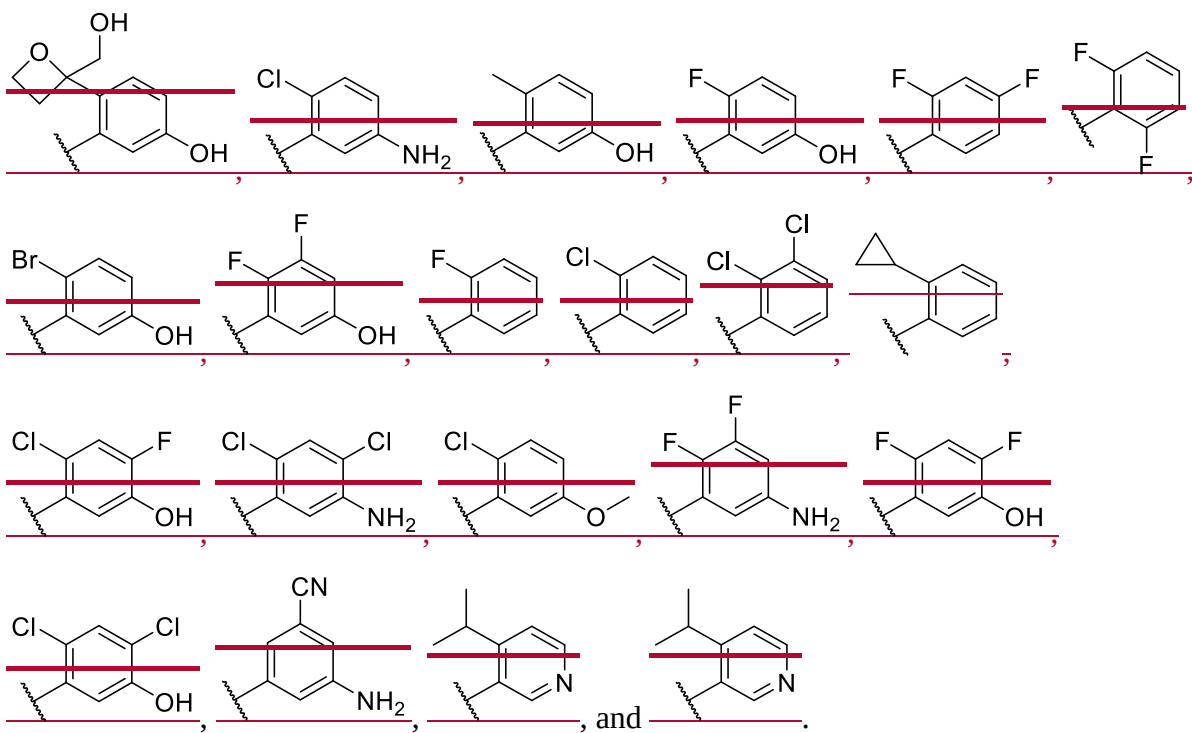
~~48~~10. The compound of any one of claims 1 to ~~479~~, wherein R^2 is aryl.

~~49.~~ The compound of any one of claims 1 to 47, wherein R^2 is heteroaryl.

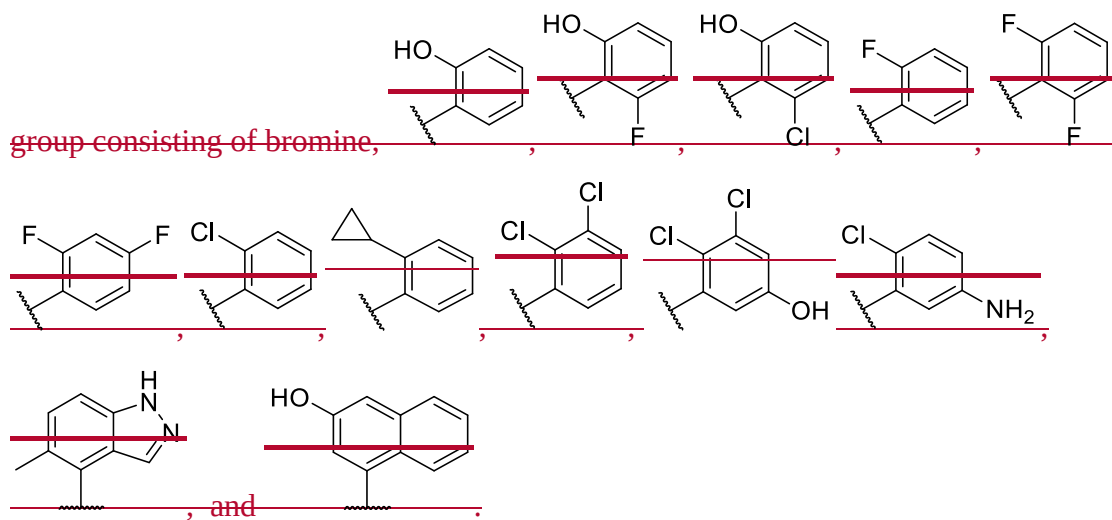
12. The compound of claim 10, wherein R² is phenyl substituted with one or more groups independently selected from halo and -OH.

group consisting of Cl, Br, CF₃, OCH₃, OCH₂CH₃, phenyl,





~~52. The compound of any one of claims 1 to 47, wherein R² is selected from the~~



~~5314. The compound of any one of claims 1 to 5212, wherein R³ is halo.~~

~~15. The compound of claim 13, wherein R³ is F.~~

~~54. The compound of claim 53, wherein R³ is Cl.~~

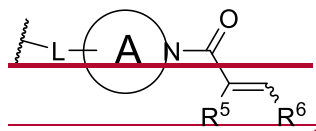
~~55. The compound of any one of claims 1 to 52, wherein R³ is
 C₁₋₂alkyl.~~

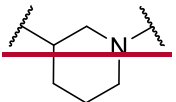
~~56. The compound of claim 55, wherein R³ is methyl.~~

~~57. The compound of any one of claims 1 to 52, wherein R³ is C₁₋₂haloalkyl.~~

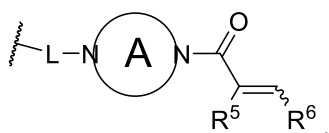
~~58. The compound of claim 57, wherein R³ is CF₃.~~

~~59. The compound of any one of claims 1 to 58, wherein R⁴ is~~

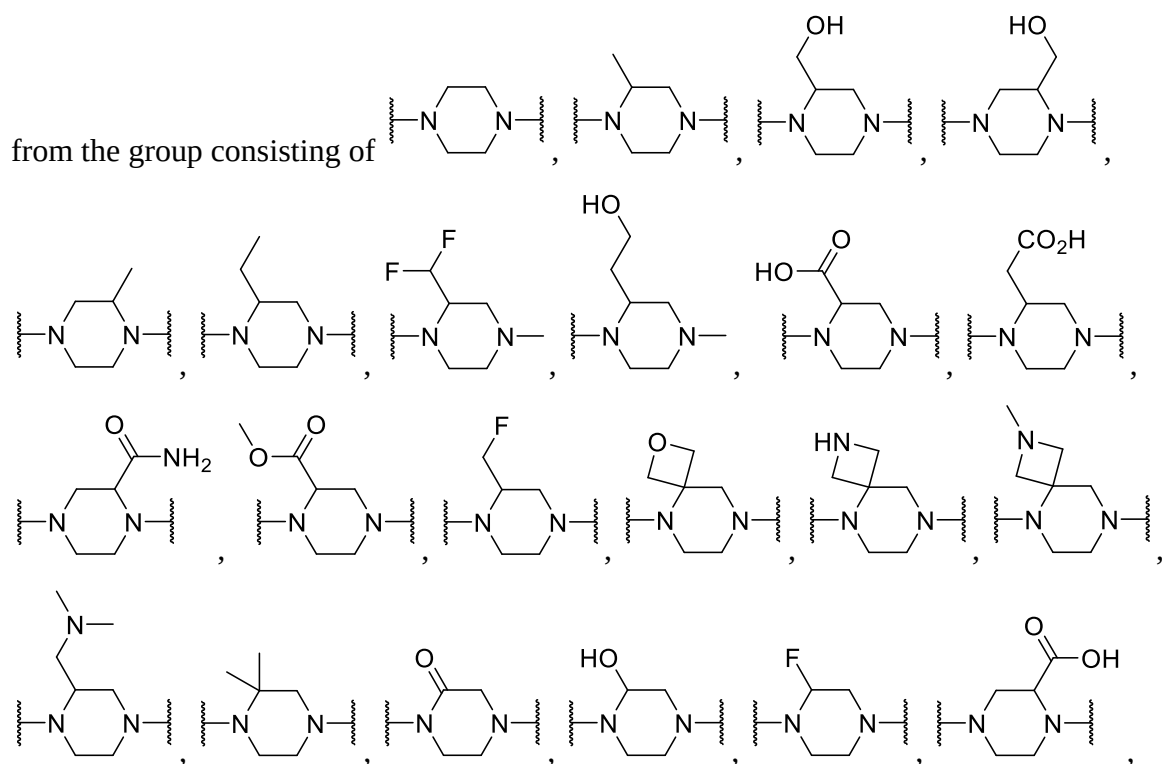


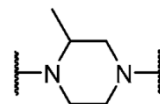
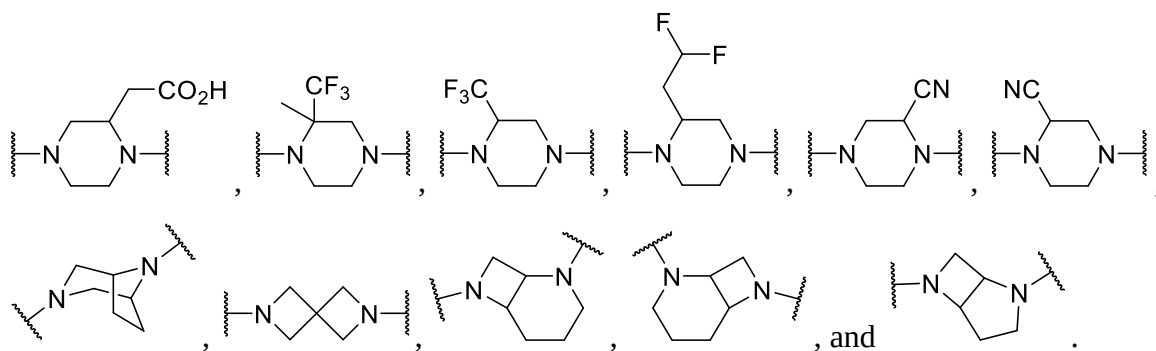
~~60. The compound of claim 59, wherein ring A is~~  ~~or~~ .

~~616.~~ The compound of any one of claims 1 to ~~58~~15, wherein R⁴ is



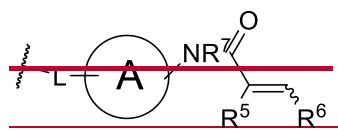
~~6217.~~ The compound of any one of ~~claims 1 to 16~~claims 1 to 64, wherein ring A is selected



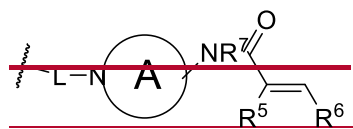


18. The compound of claim 17, wherein ring A is

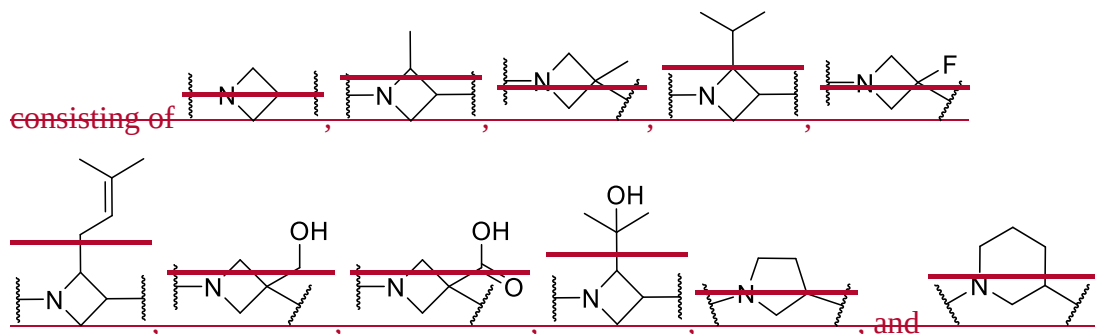
63. The compound of any one of claims 1 to 58, wherein R⁴ is



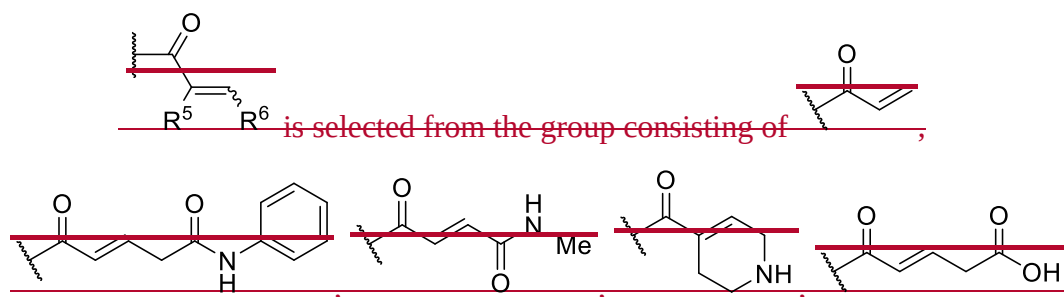
64. The compound of any one of claims 1 to 58, wherein R⁴ is

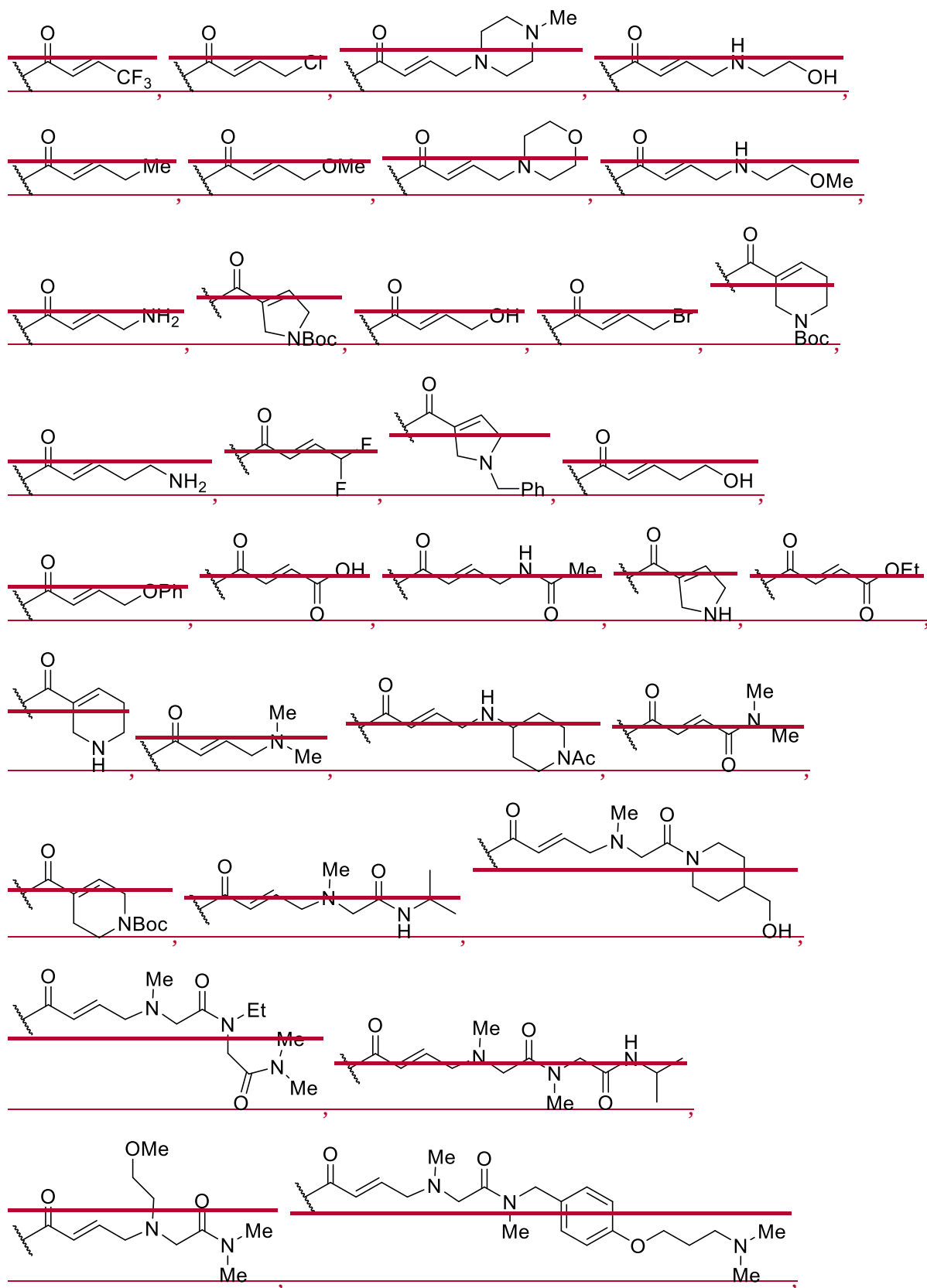


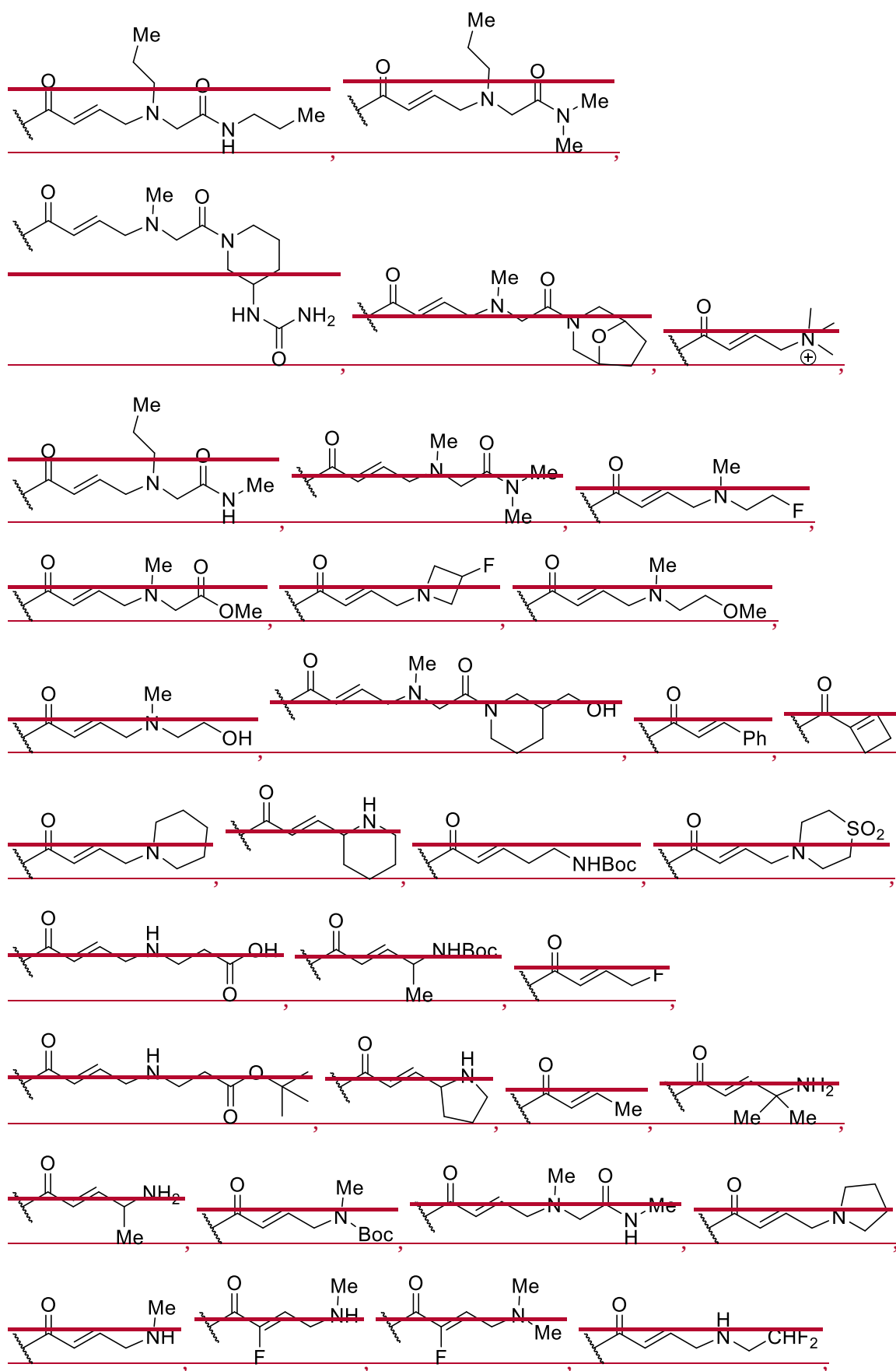
65. The compound of claim 64, wherein ring A is selected from the group

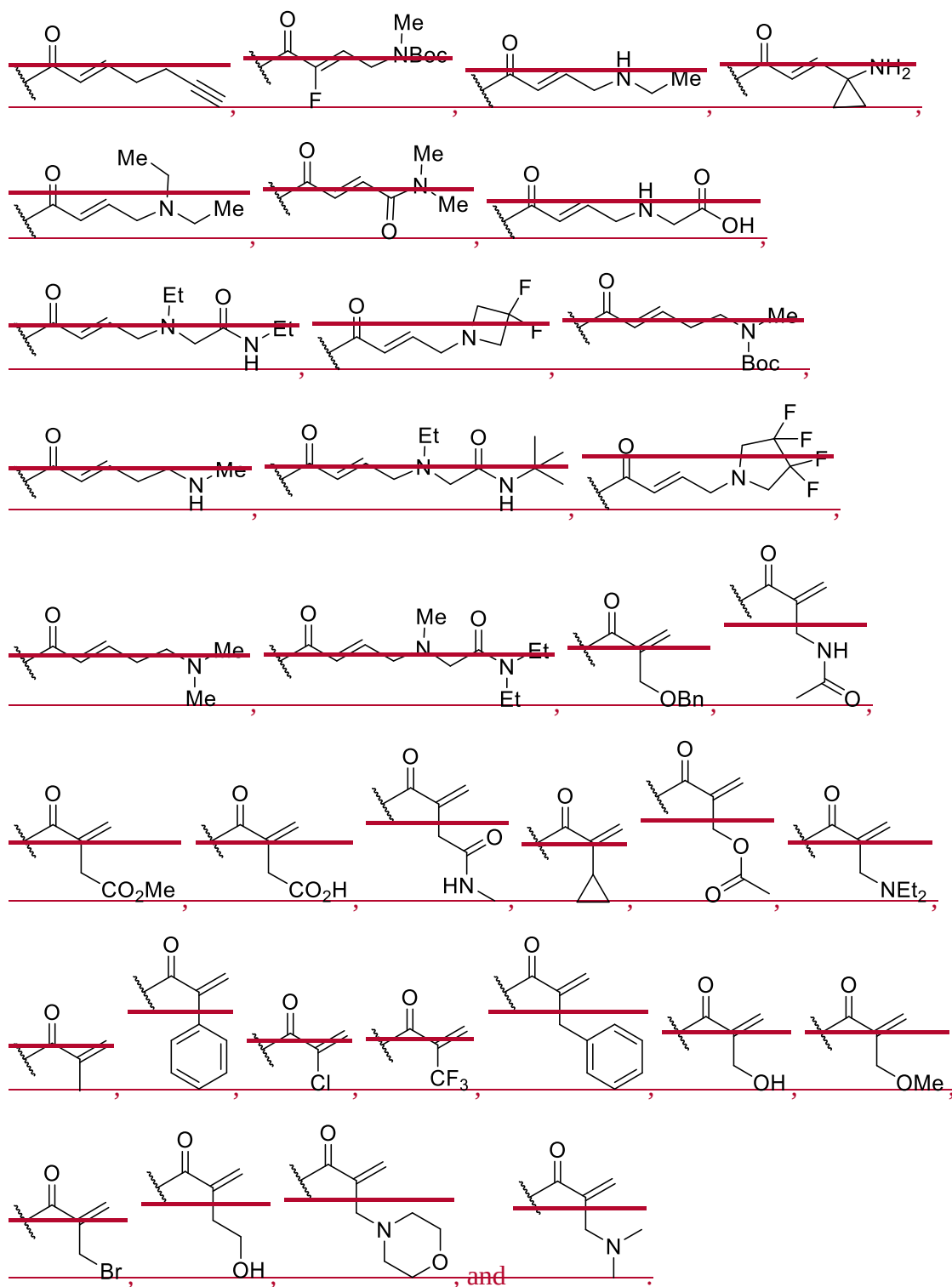


66. The compound of any one of claims 59 to 65, wherein









67. The compound of any one of claims 59 to 66, wherein L is a bond.

68. The compound of any one of claims 59 to 66, wherein L is

C_{1-2} alkylene.

69. The compound of claim 59, 60, 62, 63, or 66, wherein L is O.

~~70. The compound of claim 59, 60, 62, 63, or 66, wherein L is S.~~

~~71. The compound of claim 59, 61, 64, 65, or 66, wherein L is NH.~~

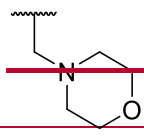
~~72~~19. The compound of any one of claims 1 to ~~59~~16, ~~61, 63, 64 and 66~~, wherein ring A comprises piperidinyl, piperazinyl, pyrrolidinyl, or azetidiny.

~~20. The compound of any one of claims 1 to 19, wherein L is a bond.~~

~~73. The compound of claim 72, wherein ring A comprises piperidinyl.~~

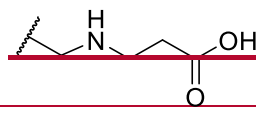
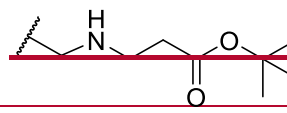
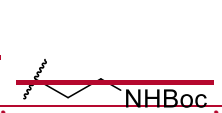
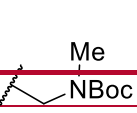
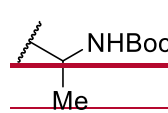
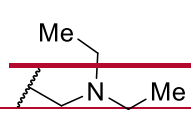
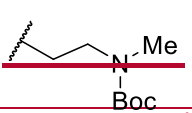
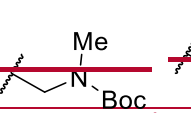
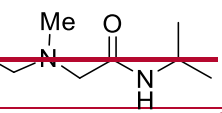
~~74. The compound of any one of claims 1 to 59, 61, 63, 64 and 65, wherein R⁵ is H or halo.~~

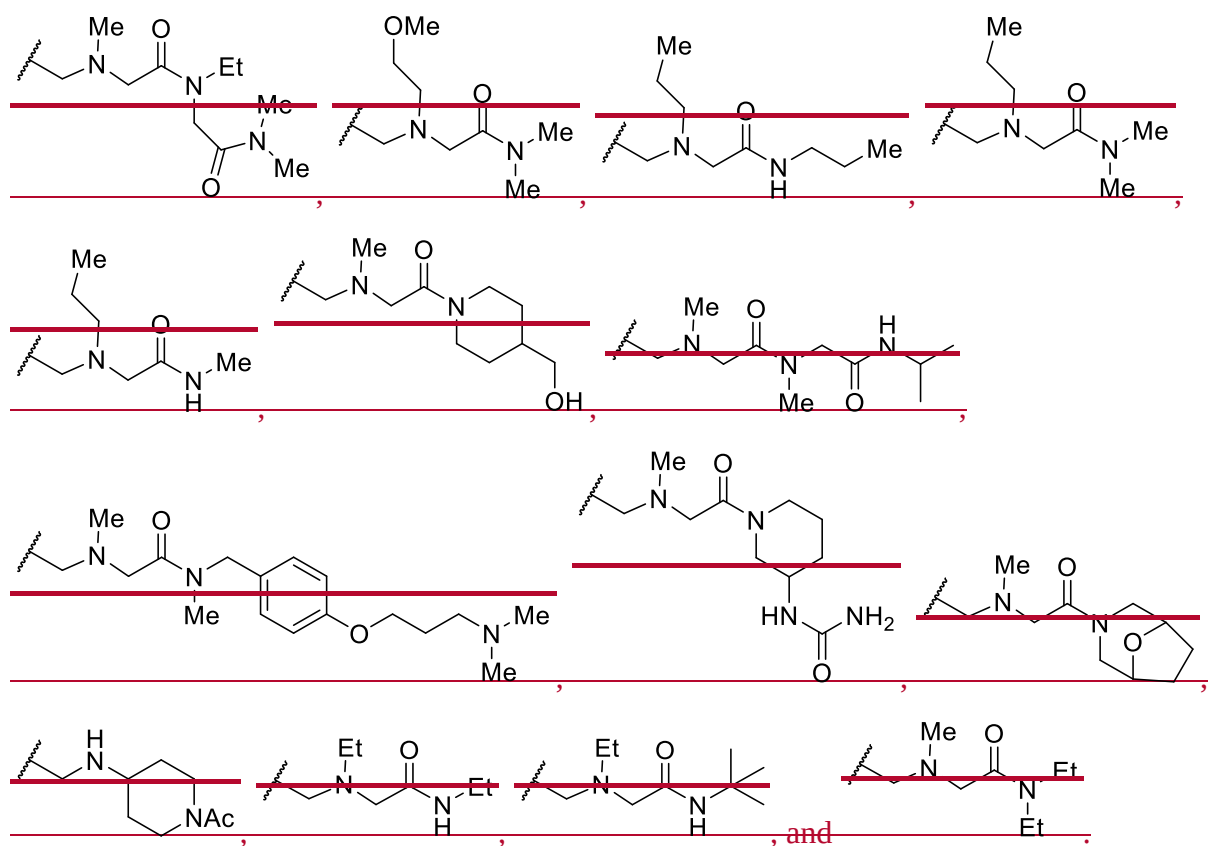
~~75. The compound of any one of claims 1 to 59, 61, 63, 64 and 65, wherein R⁵ is H, Br, Cl, F, CN, CH₃, CF₃, CH₂Br, CH₂OH, CH₂CH₂OH, CH₂OCH₂phenyl, cyclopropyl, phenyl, CH₂phenyl, CH₂OCH₃, CH₂N(CH₃)₂, CH₂N(CH₂CH₃)₂, CH₂CO₂H, CH₂CO₂CH₃,~~

~~CH₂NHC(O)CH₃, CH₂C(O)NHCH₃, CH₂OC(O)CH₃, or~~  ~~.~~

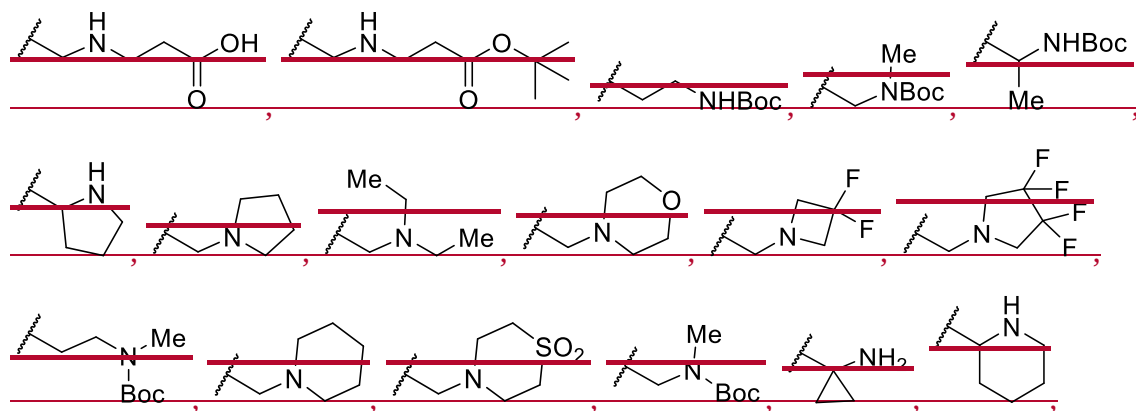
~~76. The compound of any one of claims 1 to 65 and 67 to 75, wherein R⁶ is H, C₁₋₃alkyl, C₁₋₃alkylene-O-C₁₋₂alkyl, C₁₋₃alkylene-OH, C₁₋₃haloalkyl, C₁₋₃alkylene-amine, C₀₋₃alkylene-amide, C₀₋₁alkylene-C(O)OC₁₋₃alkyl, C₀₋₁alkylene-C₂₋₇heterocycloalkyl, C₀₋₁alkylene-C₃₋₈cycloalkyl, or C₀₋₃alkylene-C₆₋₁₄aryl.~~

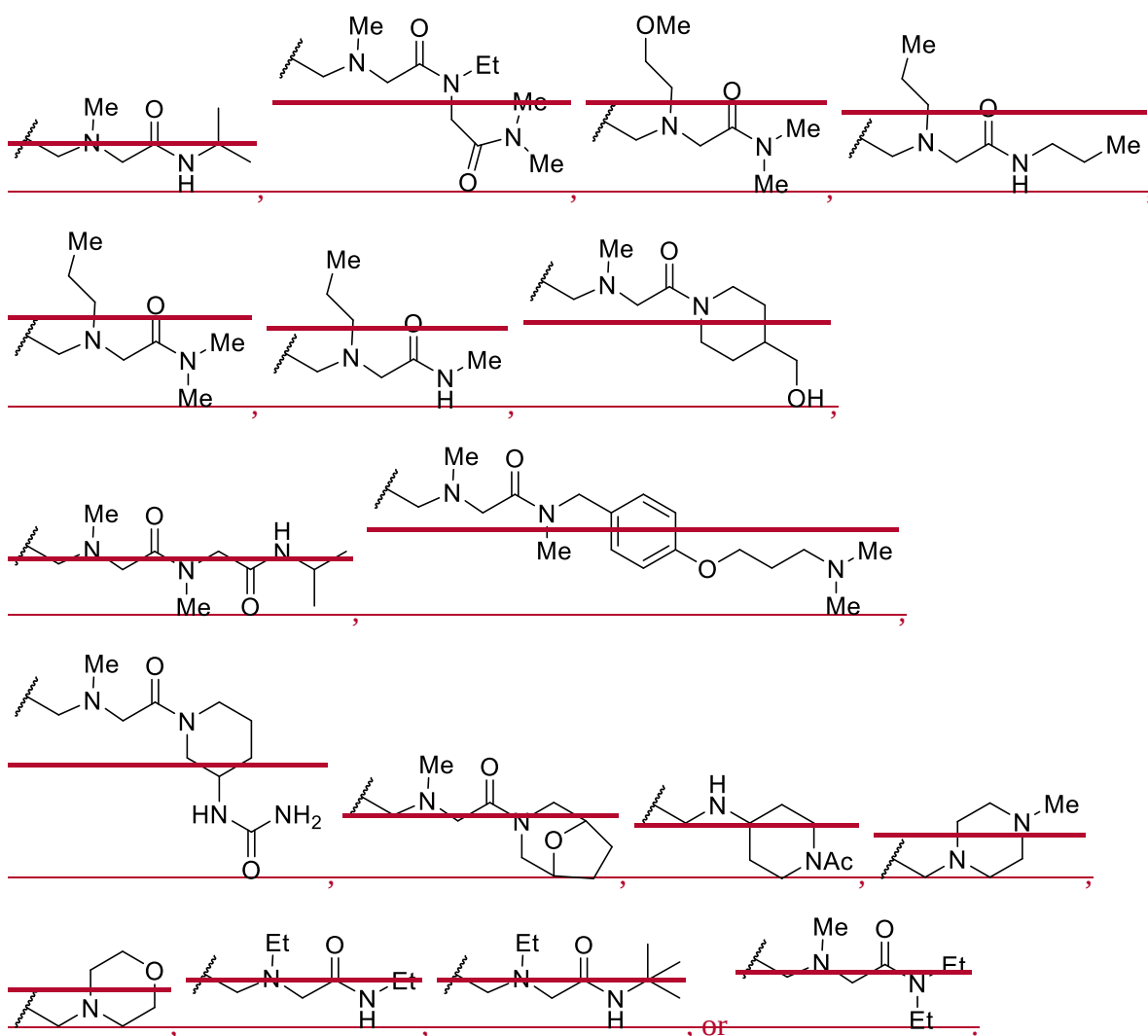
~~77. The compound of claim 76, wherein R⁶ is C₁₋₃alkylene-amine or C₁₋₃alkylene-amide and is selected from the group consisting of CH₂NH₂, CH(CH₃)NH₂, CH(CH₃)₂NH₂, CH₂CH₂NH₂, CH₂CH₂N(CH₃)₂, CH₂NHCH₃, C(O)NHCH₃, C(O)N(CH₃)₂, CH₂C(O)NHphenyl, CH₂NHC(O)CH₃, CH₂NHCH₂CH₂OH, CH₂NHCH₂CO₂H, CH₂NH(CH₃)CH₂CO₂CH₃, CH₂NHCH₂CH₂OCH₃, CH₂NH(CH₃)CH₂CH₂OCH₃, CH₂NH(CH₃)CH₂C(O)N(CH₃)₂, CH₂NH(CH₃)CH₂C(O)NHCH₃, CH₂NMe₂, CH₂NH(CH₃)CH₂CH₂OH, CH₂NH(CH₃)CH₂CH₂F, CH₂N⁺(CH₃)₃, CH₂NHCH₂CHF₂,~~

~~CH₂NHCH₂CH₃,~~ , , , , , , , , 

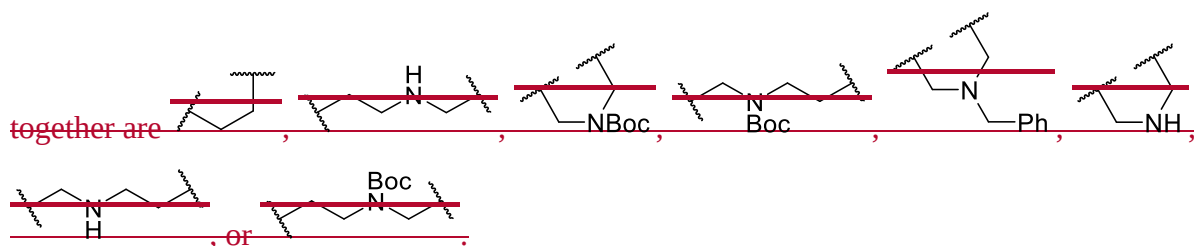


78. — The compound of any one of claims 1 to 65 and 67 to 75, wherein R^6 is phenyl, cyclopropyl, CH_3 , CF_3 , CH_2CH_3 , CH_2NH_2 , $CH(CH_3)NH_2$, $CH(CH_3)_2NH_2$, CH_2Cl , CH_2Br , CH_2OCH_3 , $CH_2Ophenyl$, CH_2OH , CO_2H , $CO_2CH_2CH_3$, CH_2CO_2H , $CH_2CH_2NH_2$, CH_2CH_2OH , $CH_2CH_2N(CH_3)_2$, CH_2NHCH_3 , $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $CH_2C(O)NHphenyl$, CH_2CHF_2 , CH_2F , CHF_2 , $CH_2NHC(O)CH_3$, $CH_2NHCH_2CH_2OH$, $CH_2NHCH_2CO_2H$, $CH_2NH(CH_3)CH_2CO_2CH_3$, $CH_2NHCH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2C(O)N(CH_3)_2$, $CH_2NH(CH_3)CH_2C(O)NHCH_3$, $CH_2CH_2CCH_3$, CH_2NMe_2 , $CH_2NH(CH_3)CH_2CH_2OH$, $CH_2NH(CH_3)CH_2CH_2F$, $CH_2N^+(CH_3)_3$, $CH_2NHCH_2CHF_2$, $CH_2NHCH_2CH_3$,





~~79. The compound of any one of claims 1 to 65 and 67 to 73, wherein R^5 and R^6~~



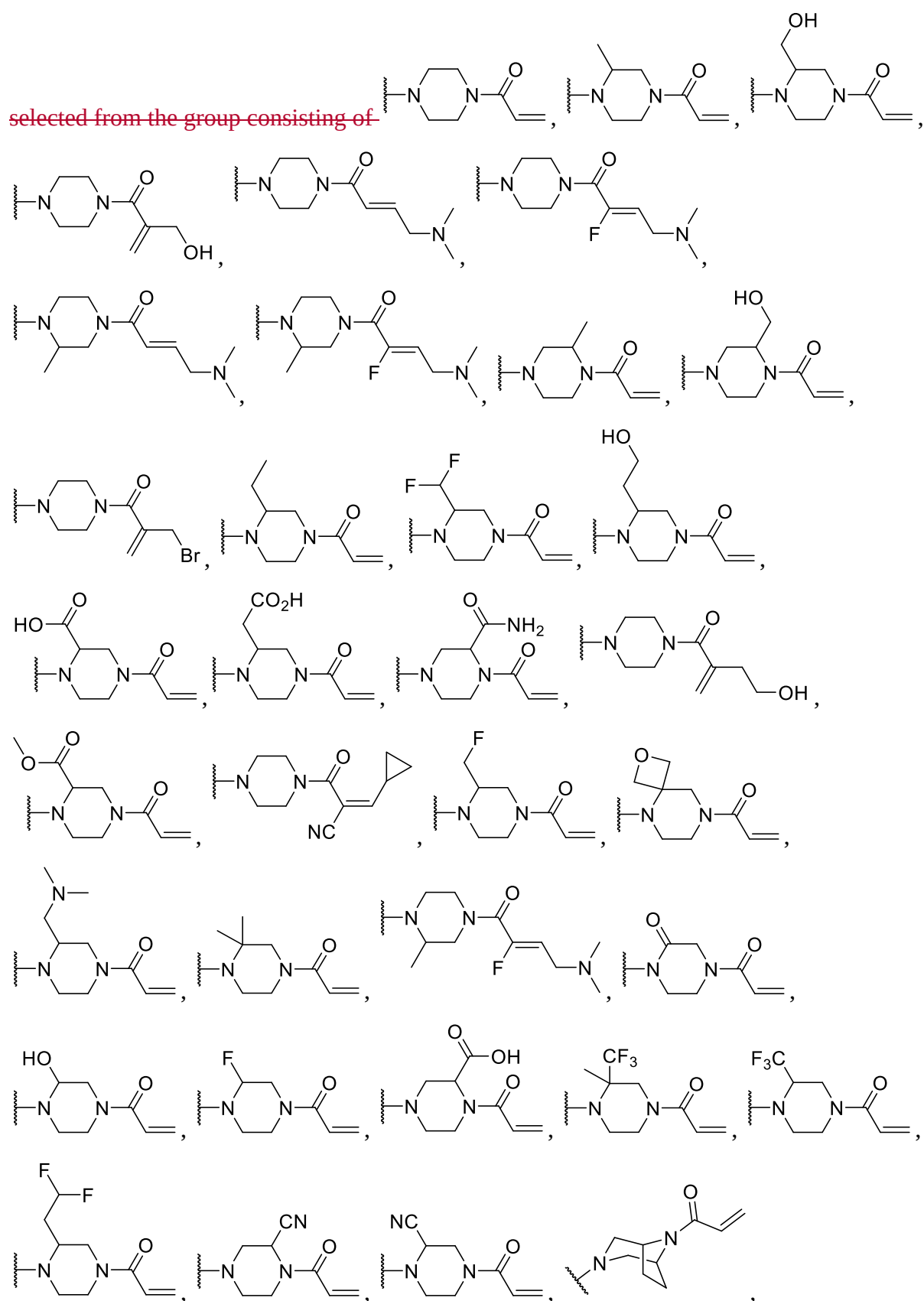
~~80~~21. The compound of any one of claims 1 to ~~65-20~~and 67 to 73, wherein each of R^5 and R^6 is H.

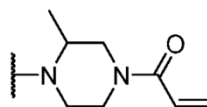
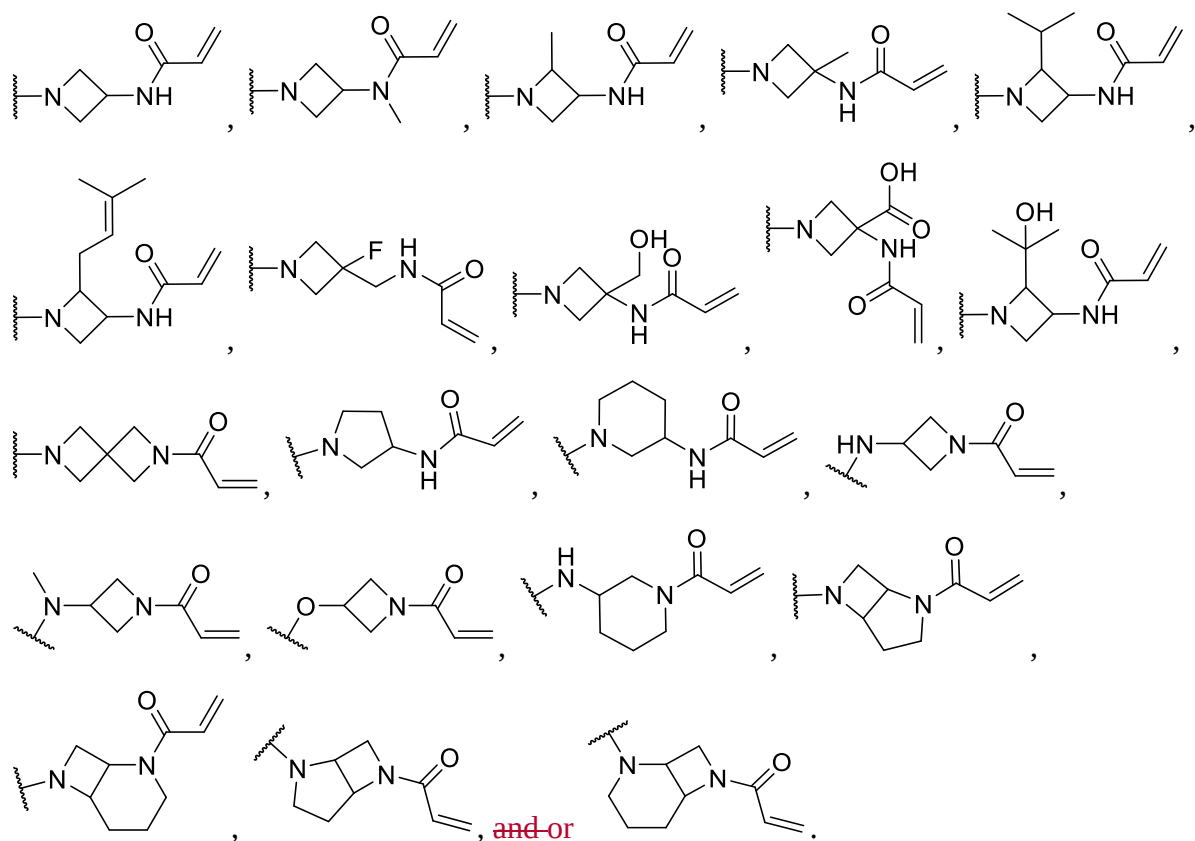
~~81. The compound of any one of claims 1 to 58 and 63 to 80, wherein R^7 is H.~~

~~82. The compound of any one of claims 1 to 58 and 63 to 80, wherein R^7 is methyl.~~

~~83. The compound of any one of claims 1 to 58, 63 to 65, 67-73 and 76 to 78, wherein R^7 and R^5 together are CH_2 or $C(O)CH_2$.~~

8422. The compound of any one of claims 1 to 15, 20 and 2158, wherein R⁴ is





23. The compound of claim 22, wherein R⁴ is

85. A compound as recited in Table 1.

86. The compound of any one of claims 1 to 85 in the form of a pharmaceutically acceptable salt.

8724. A pharmaceutical formulation comprising the compound of any one of claims 1 to 86-23 and a pharmaceutically acceptable excipient.

8825. An in vitro method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 1 to 86-23 or the pharmaceutical formulation of claim 8724.

8926. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount Use of the compound of any one of claims 1 to 86-23 or the pharmaceutical formulation of claim 8724 in the manufacture of a medicament for treating cancer.

9027. The ~~method-use~~ of claim 8926, wherein the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

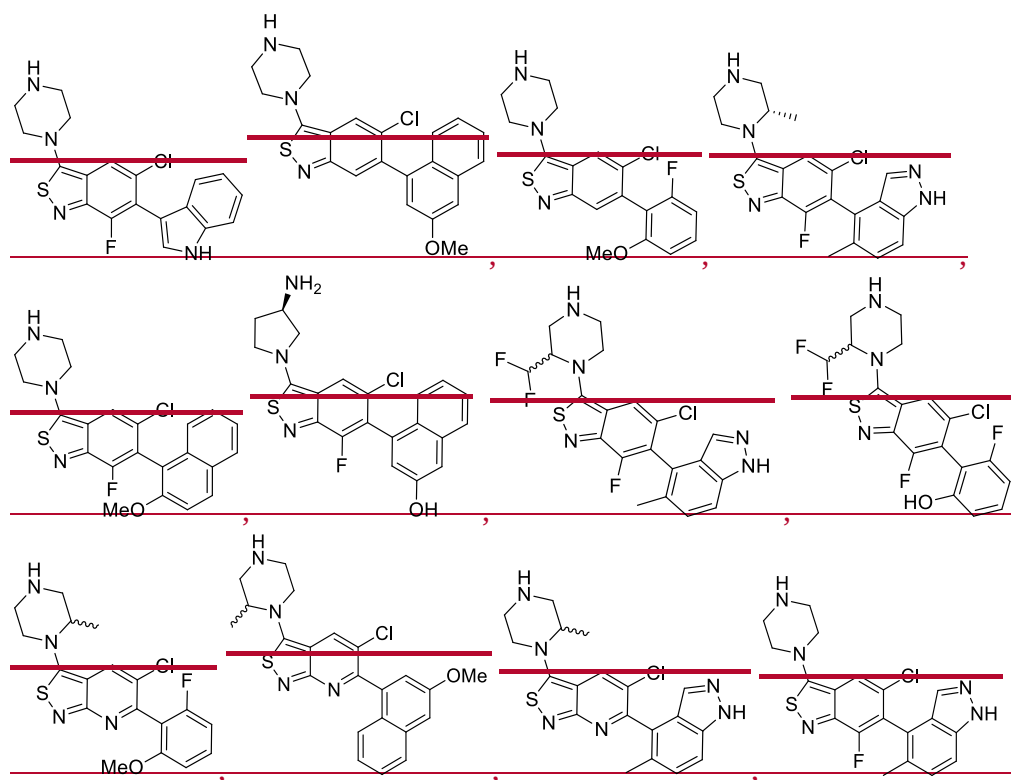
28. The use of claim 27 wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

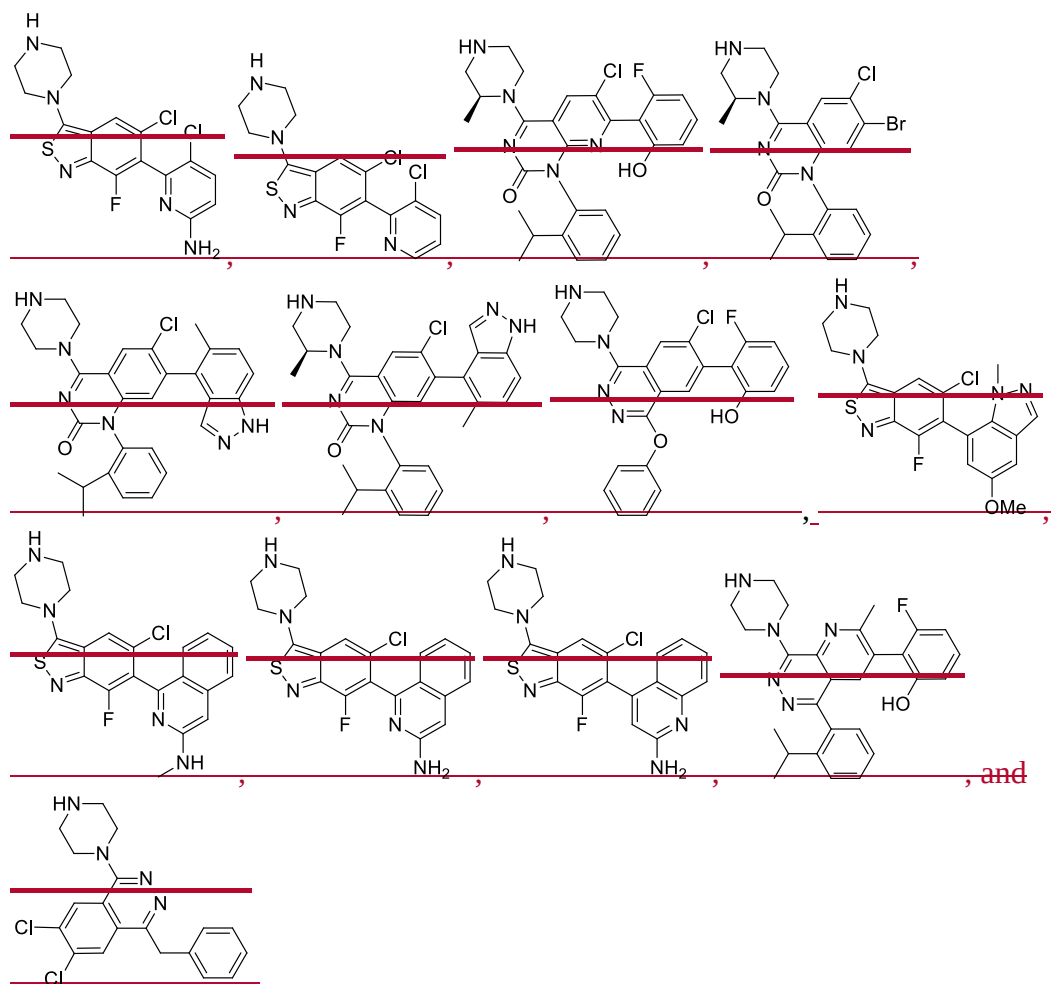
29. The use of claim 27, wherein the cancer is non-small cell lung cancer.

30. The use of claim 27, wherein the cancer is colorectal cancer.

31. The use of any one of claims 27 to 30, wherein the cancer is mediated by a KRAS G12C mutation.

91.—A compound having a structure selected from:





92. ~~The compounds of claim 91 in the form of a pharmaceutically acceptable salt.~~

93. ~~A pharmaceutical formulation comprising the compounds of claim 91 or 92 and a pharmaceutically acceptable excipient.~~