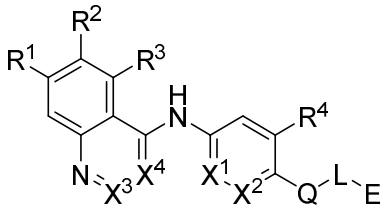
of avapritinib is also limited due to central nervous system (CNS) adverse events that resulted in black box label restriction.

[0006] There is a clear unmet need for a tyrosine kinase inhibitor with potent inhibitory activity against a broad spectrum of clinically relevant KIT and PDGFRA mutants, and an improved safety and tolerability profile when compared to currently available GIST treatments.

SUMMARY

[0007] Described herein, in part, are compounds that are inhibitors of wild type and oncogenic mutant c-KIT kinase and methods of use thereof, such as the treatment of cancers driven by c-KIT kinase mutations, e.g., primary (*KIT* exon 9 or 11) and secondary (exons 13, 14, 17 and 18) c-KIT mutations.

[0008] In one example, described herein, is a compound represented by Formula I:



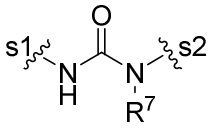
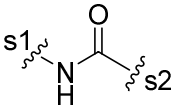
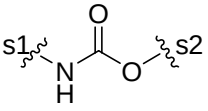
Formula I

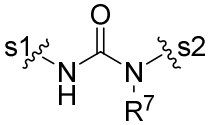
or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

X^3 and X^4 are each independently CH or N, provided that not more that one of X^3 and X^4 is N;

Q is selected from the group consisting of

 ,  , and  , wherein s1 is the site covalently linked to the ring; and s2 is the site covalently linked to L;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$, or when Q is  , L taken together with R^7 and the N atom to which L and R^7 are attached form an optionally substituted heterocyclyl having from 4 to 10 atoms in the ring structure wherein the optional substituent is selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{10} is selected from the group consisting of H and alkyl, or taken together with R^8 and the N atom to which R^8 and R^{10} are attached form an optionally substituted heterocyclyl having from 4 to 8 atoms in the ring structure wherein the optional substituent at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

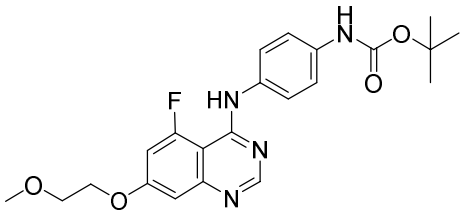
R^{11} is selected from the group consisting of H and alkyl, or taken together with R^9 and the atoms to which R^9 and R^{11} are respectively attached form an optionally substituted heterocyclyl having from 4 to 7 atoms in the ring structure wherein the optional substituent, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, and haloalkoxy;

each occurrence of m is independently 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

p is 1, 2, or 3,

provided that the compound is not:



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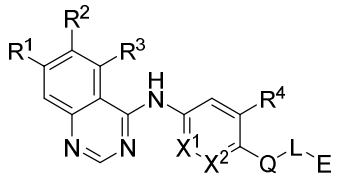
[0008a] In one aspect, the present disclosure refers to a compound represented by Formula I-A:

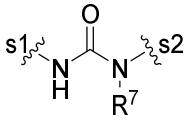


Formula I-A

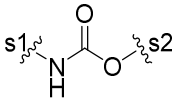
or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF

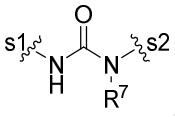
Q is selected from the group consisting of



, and



, wherein s1 is the site covalently linked to the ring; and s2 is the site covalently linked to L;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$, or when Q is  , L when taken together with R^7 and the N atom to which L and R^7 are attached form an optionally substituted heterocyclyl having from 4 to 10 atoms in the ring structure wherein the optional substituent is selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

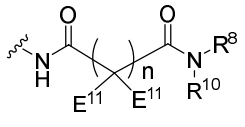
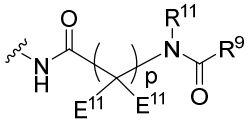
E is selected from the group consisting of H, alkenyl, cyano, alkoxy, haloalkoxy, haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl; or

Q-L-E taken together is selected from the group consisting of  and  ;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^1 is selected from the group consisting of H,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently, C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

optionally substituted cycloalkyloxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, amine, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

optionally substituted heterocyclyloxy wherein the optionally substituted substituent, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo, and

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkoxy, and hydroxy;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^1 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^7 is selected independently from the group consisting of H, alkyl, haloalkyl, or cycloalkyl;

R^8 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{10} is selected from the group consisting of H and alkyl, or taken together with R^8 and the N atom to which R^8 and R^{10} are attached form an optionally substituted heterocyclyl having from 4 to 8 atoms in the ring structure wherein the optional substituent is, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

R^{11} is selected from the group consisting of H and alkyl, or taken together with R^9 and the atoms to which R^9 and R^{11} are respectively attached form an optionally substituted heterocyclyl having from 4 to 7 atoms in the ring structure wherein the optional substituent, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, and haloalkoxy;

each occurrence of m is independently 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

p is 1, 2, or 3; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

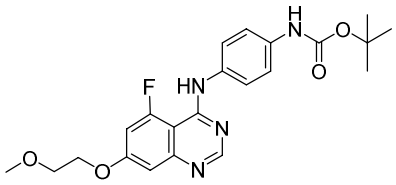
each cycloalkyl is C_3-C_{10} cycloalkyl;

each cycloalkyloxy is C_3-C_6 cycloalkyloxy;

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms;

provided that the compound is not:



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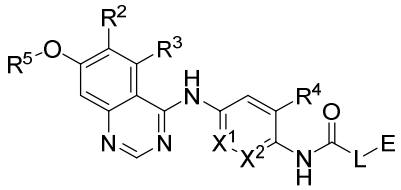
[0008b] In one aspect, the present disclosure refers to a compound

(i) represented by Formula I-T:



Formula I-T

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$;

E is selected from the group consisting of

optionally substituted amido wherein the substituent, at each occurrence, is independently, selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano,

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of cycloalkyl and heterocyclyl,

H, cyano, alkoxy, haloalkoxy, haloalkyl, and halogen;

E^{11}, at each occurrence, is independently, selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen; and

each occurrence of m is independently 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

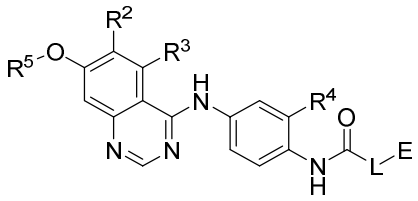
each cycloalkyl is C_3-C_{10} cycloalkyl;

each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms; or

(ii) represented by Formula I-U:



Formula I-U

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$;

E is selected from the group consisting of

optionally substituted amido wherein the substituent, at each occurrence, is independently, selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano,

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of cycloalkyl, heterocyclyl,

H, cyano, alkoxy, haloalkoxy, haloalkyl, and halogen;

E^{11}, at each occurrence, is independently, selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted

substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen; and

each occurrence of m is independently 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

each cycloalkyl is C_3-C_{10} cycloalkyl;

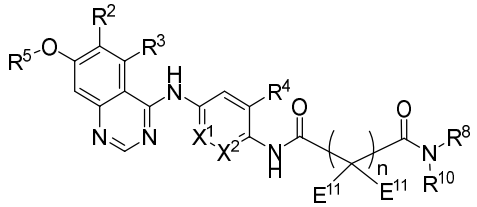
each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms.

[0008c] In one aspect, the present disclosure refers to a compound

(i) represented by Formula I-X:



Formula I-X

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which

they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen;

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^8 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{10} is selected from the group consisting of H and alkyl, or taken together with R^8 and the N atom to which R^8 and R^{10} are attached form an optionally substituted heterocyclyl having from 4 to 8 atoms in the ring structure wherein the optional substituent is, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo; and

n is 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

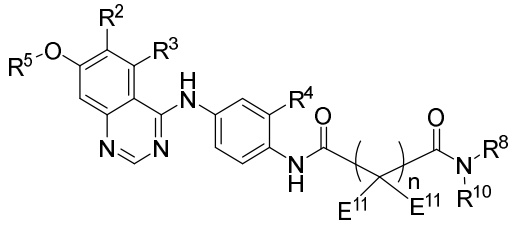
each cycloalkyl is C_3-C_{10} cycloalkyl;

each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

wherein each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms; or

(ii) represented by Formula I-Y:



Formula I-Y

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen;

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^8 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{10} is selected from the group consisting of H and alkyl, or taken together with R^8 and the N atom to which R^8 and R^{10} are attached form an optionally substituted heterocyclyl having from 4 to 8 atoms in the ring structure wherein the optional substituent is, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo; and

n is 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

each cycloalkyl is C_3-C_{10} cycloalkyl;

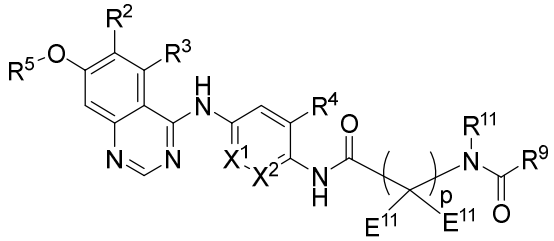
each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms.

[0008d] In one aspect, the present disclosure refers to a compound

(i) represented by Formula I-AB:



Formula I-AB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy,

amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{11} is selected from the group consisting of H and alkyl, or taken together with R^9 and the atoms to which R^9 and R^{11} are respectively attached form an optionally substituted heterocyclyl having from 4 to 7 atoms in the ring structure wherein the optional substituent, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, and haloalkoxy; and

p is 1, 2, or 3; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

each cycloalkyl is C_3-C_{10} cycloalkyl;

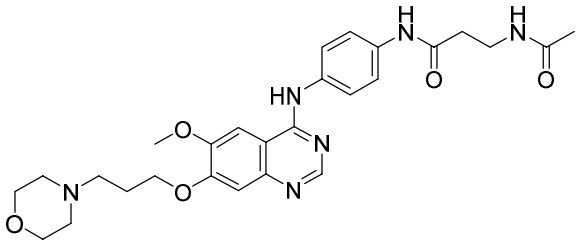
each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to

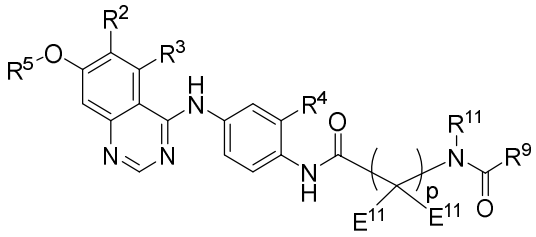
10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms;

provided that the compound is not:



; or

(ii) represented by Formula I-AC:



Formula I-AC

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{11} is selected from the group consisting of H and alkyl, or taken together with R^9 and the atoms to which R^9 and R^{11} are respectively attached form an optionally substituted heterocyclyl having from 4 to 7 atoms in the ring structure wherein the optional substituent, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, and haloalkoxy; and

p is 1, 2, or 3; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

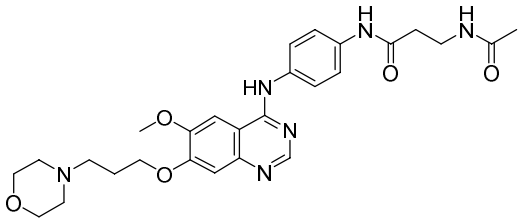
each cycloalkyl is C_3-C_{10} cycloalkyl;

each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms;

provided that the compound is not:



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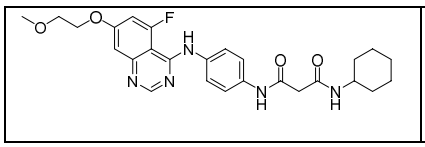
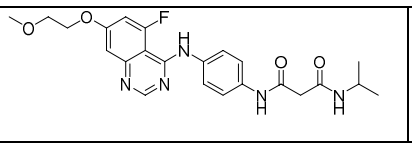
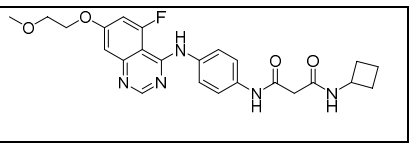
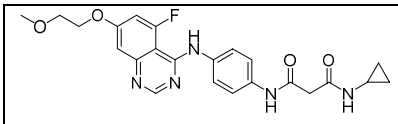
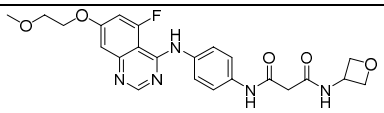
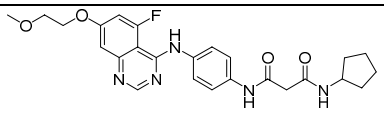
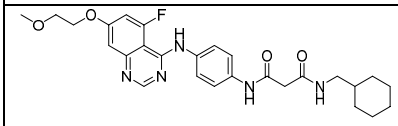
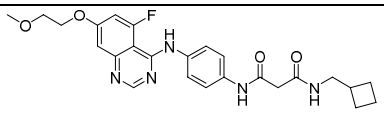
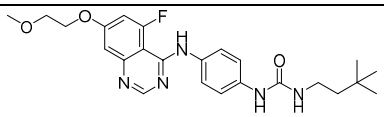
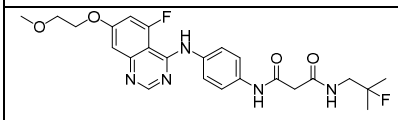
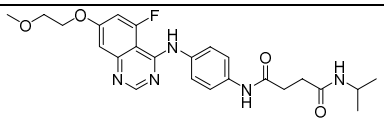
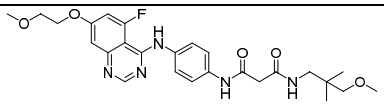
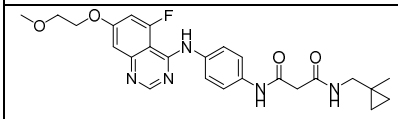
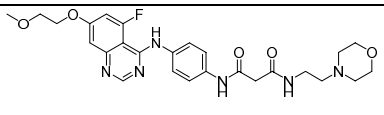
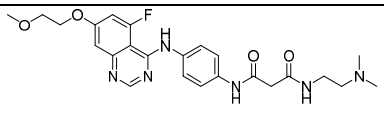
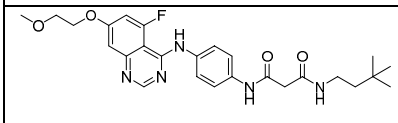
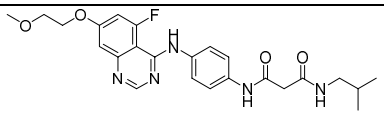
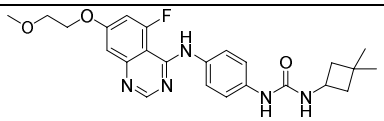
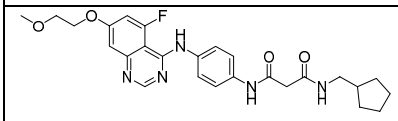
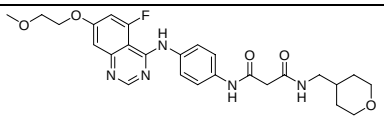
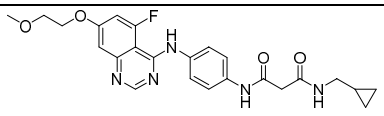
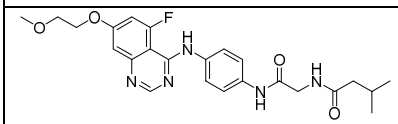
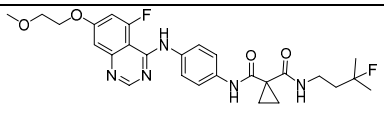
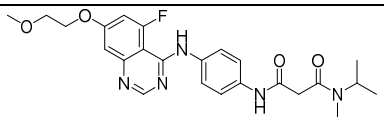
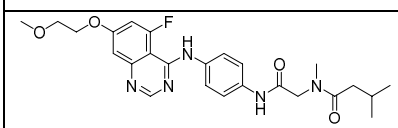
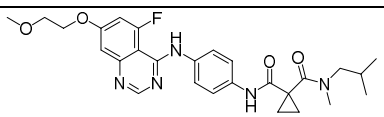
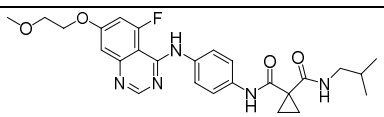
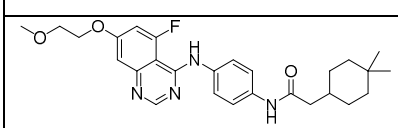
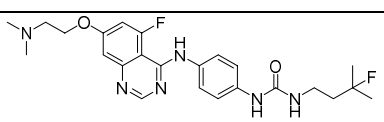
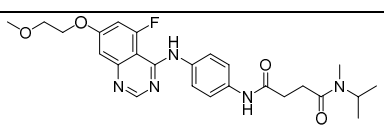
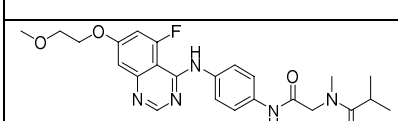
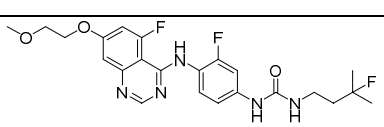
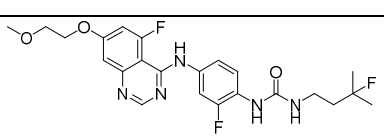
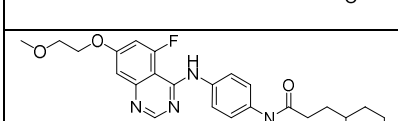
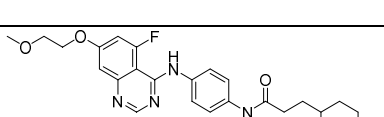
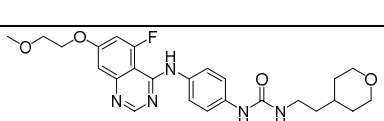
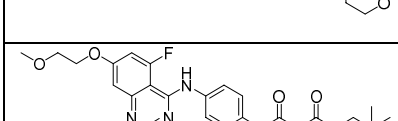
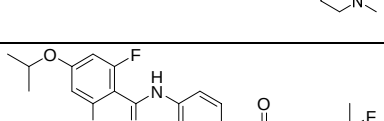
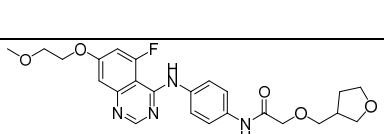
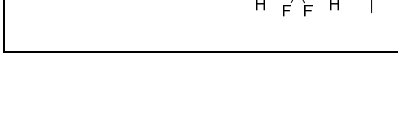
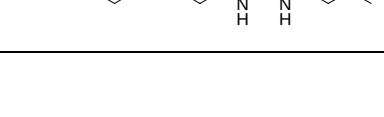
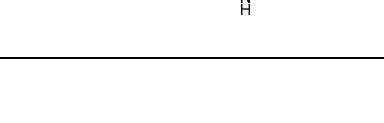
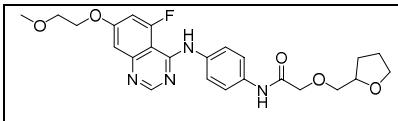
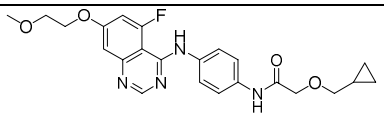
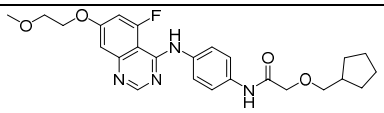
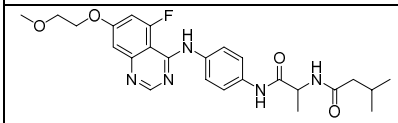
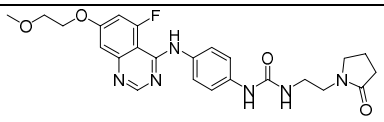
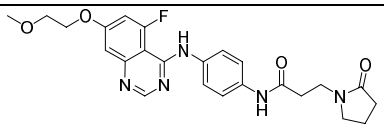
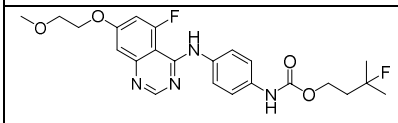
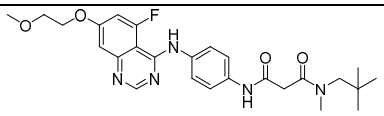
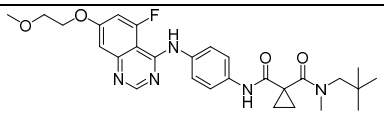
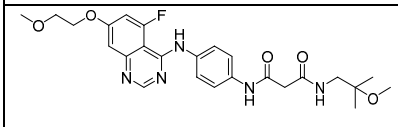
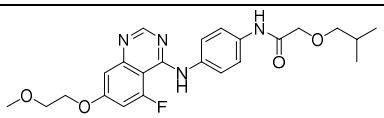
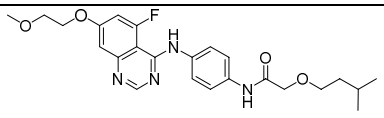
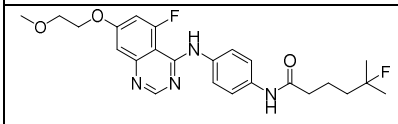
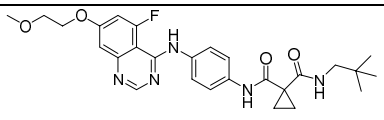
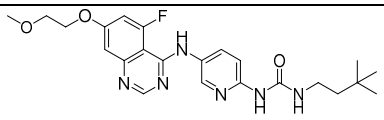
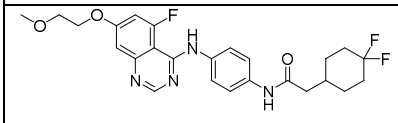
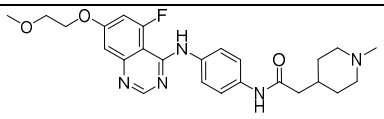
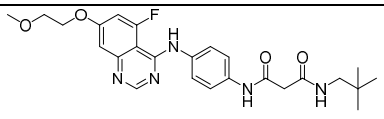
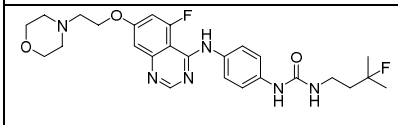
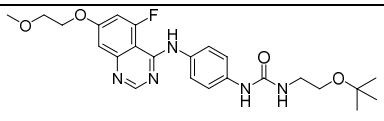
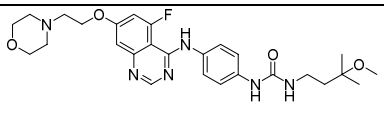
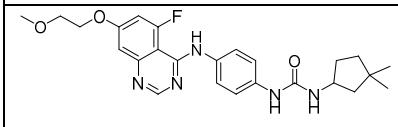
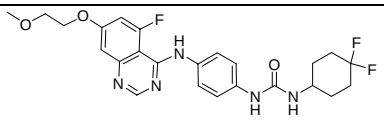
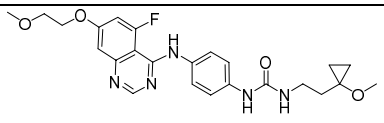
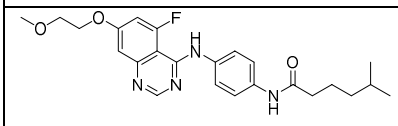
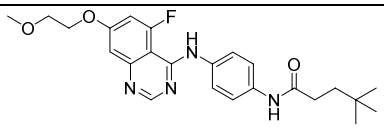
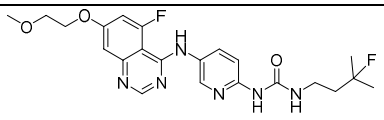
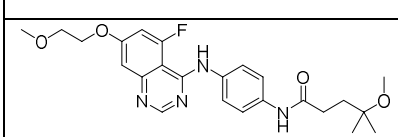
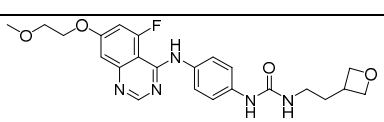
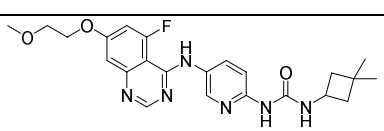
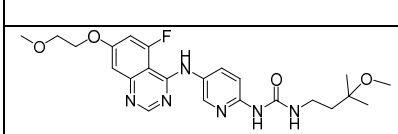
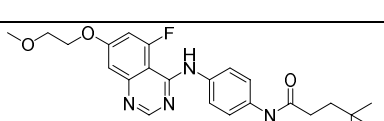
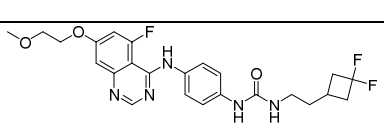
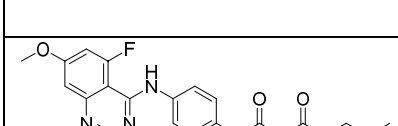
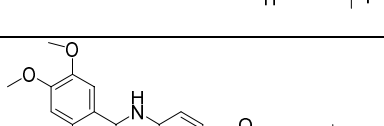
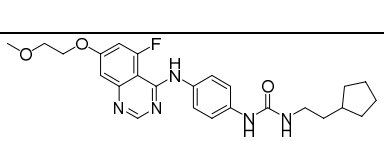
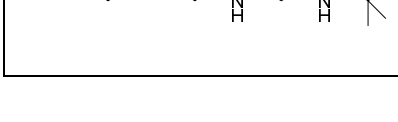
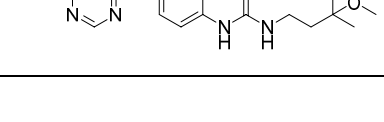
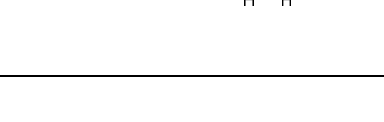
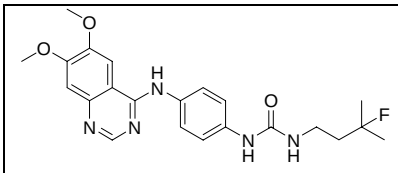
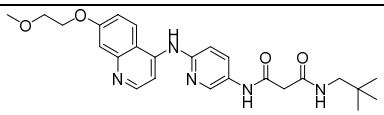
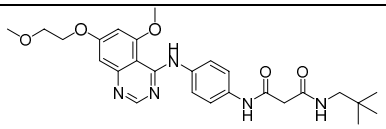
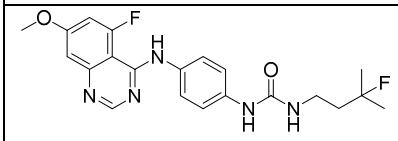
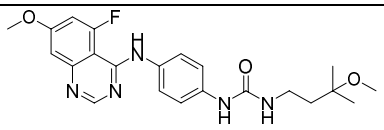
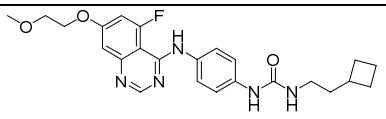
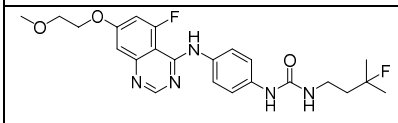
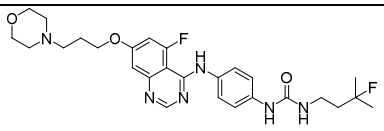
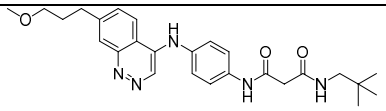
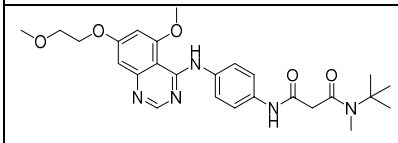
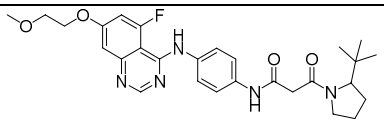
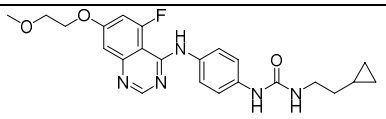
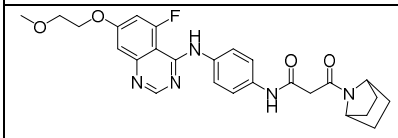
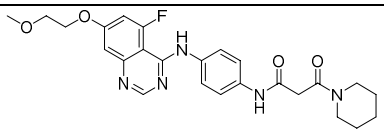
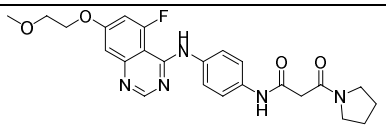
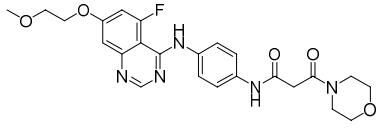
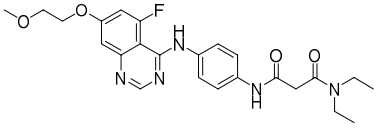
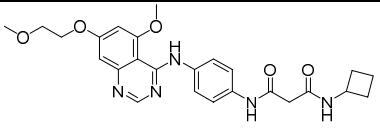
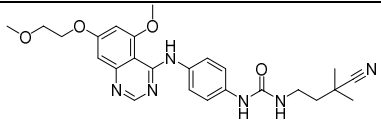
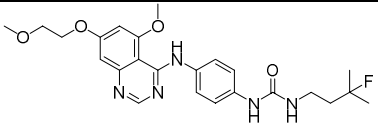
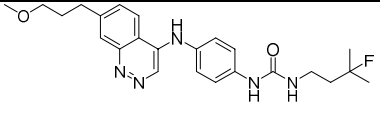
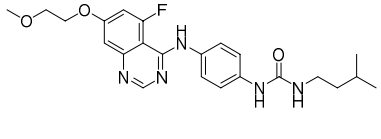
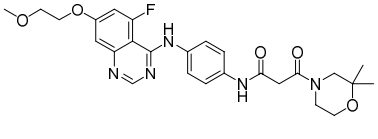
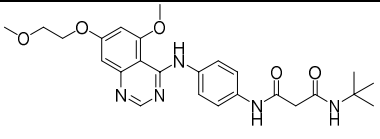
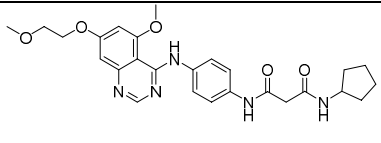
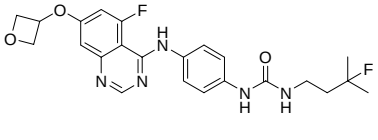
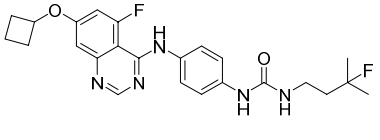
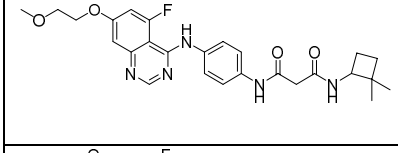
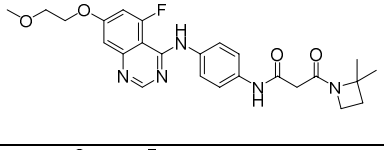
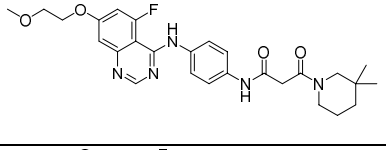
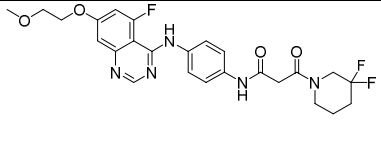
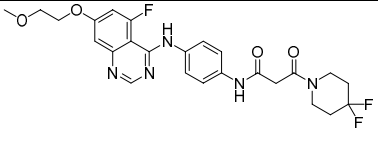
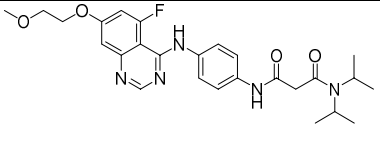
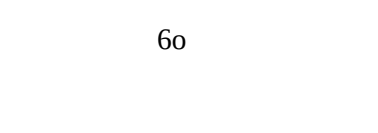
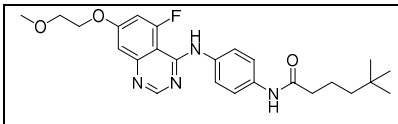
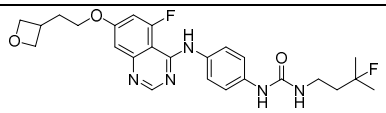
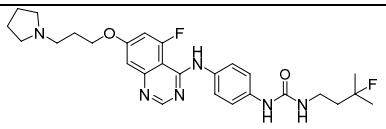
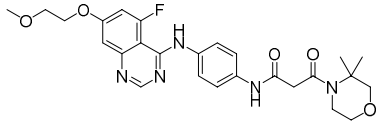
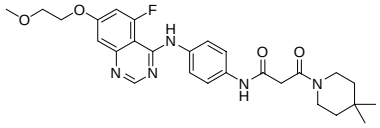
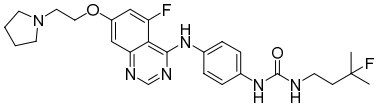
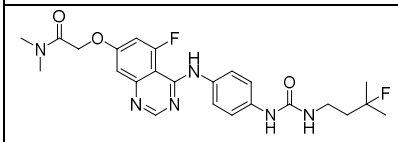
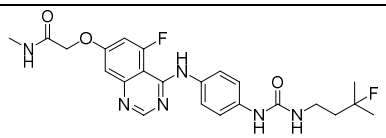
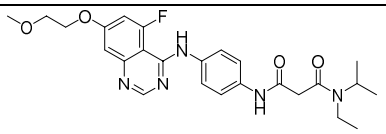
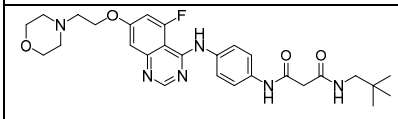
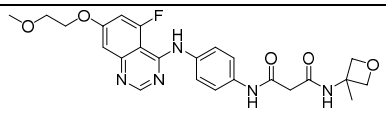
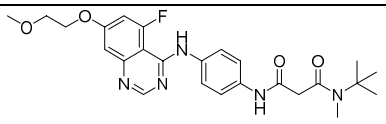
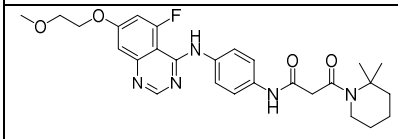
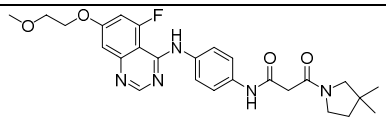
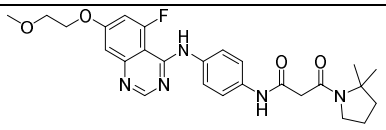
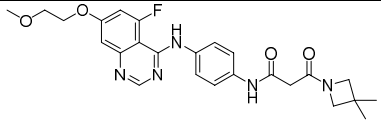
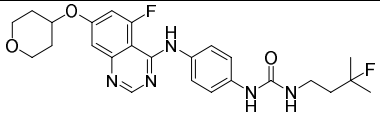
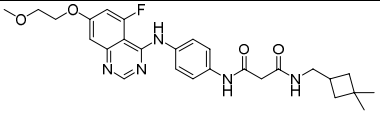
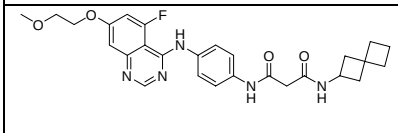
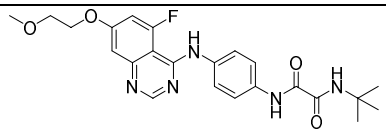
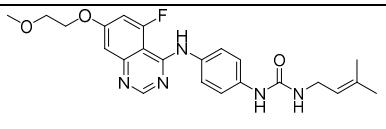
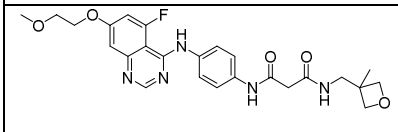
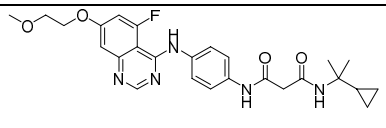
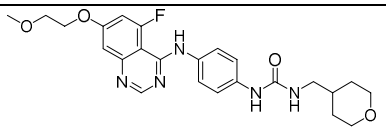
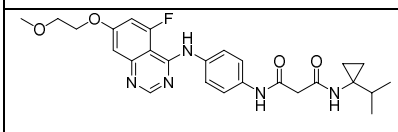
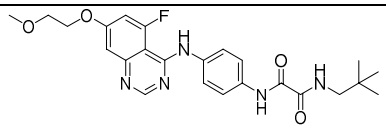
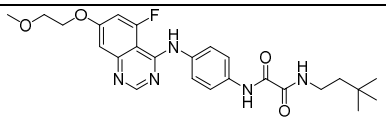
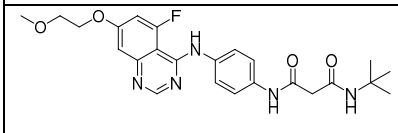
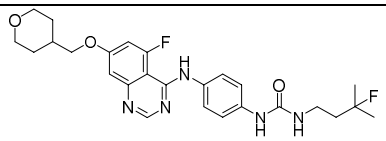
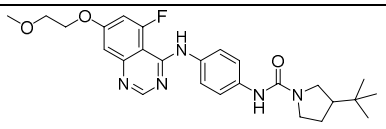
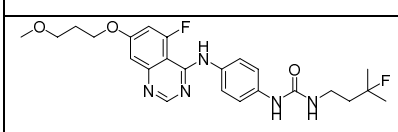
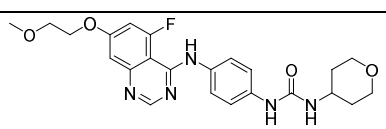
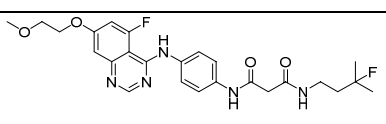
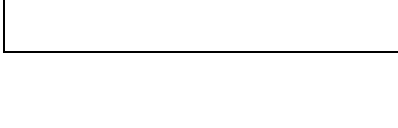
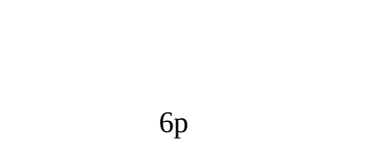
[0008e] In one aspect, the present disclosure refers to a compound selected from:

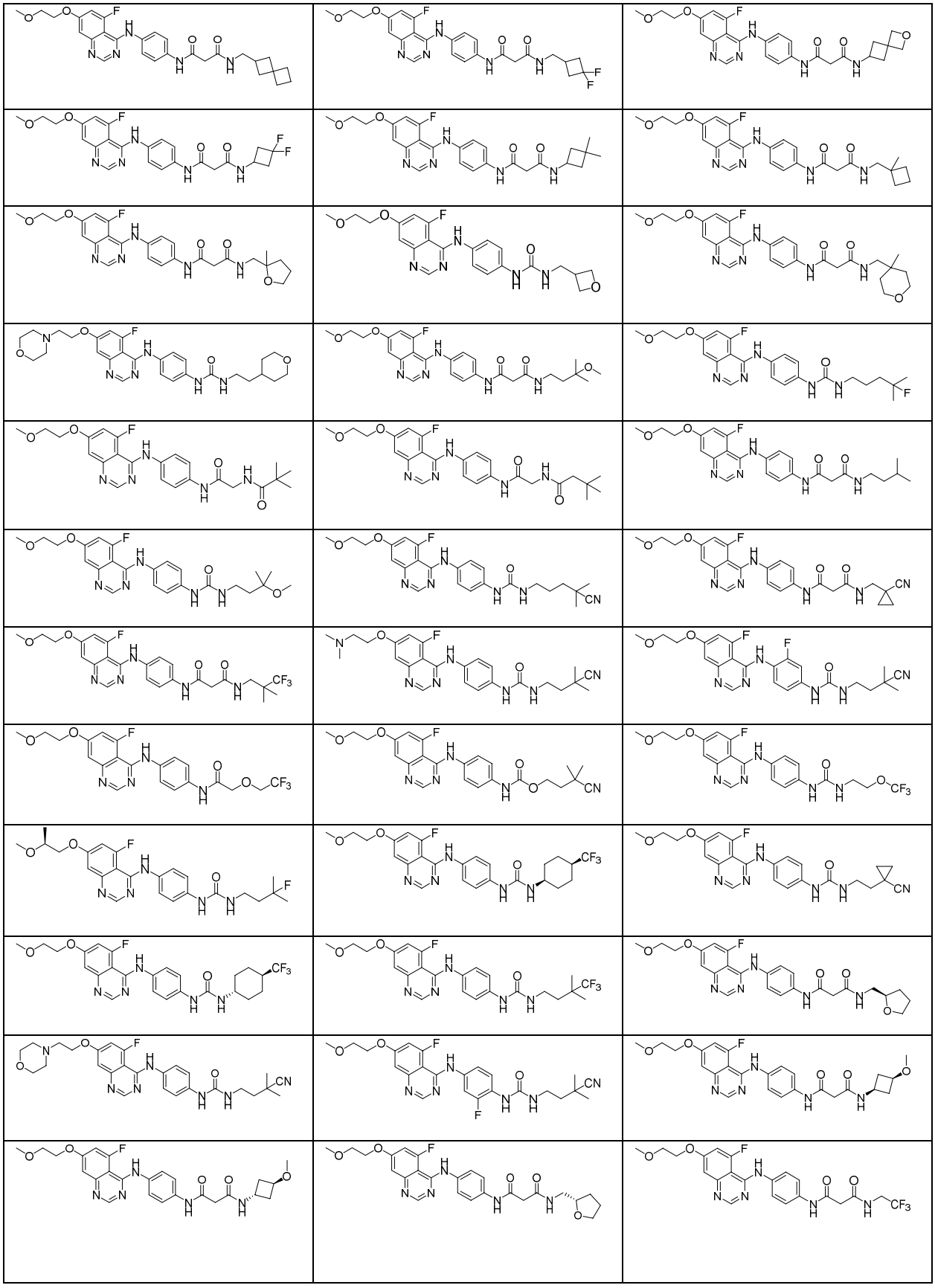




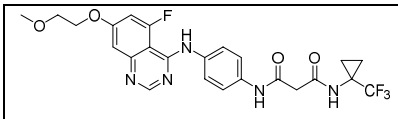
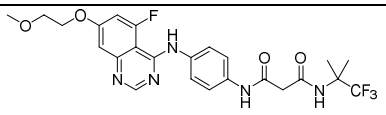
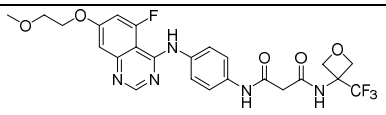
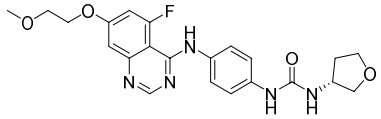
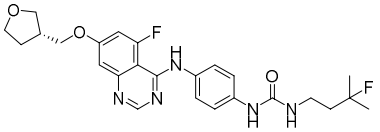
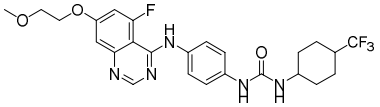
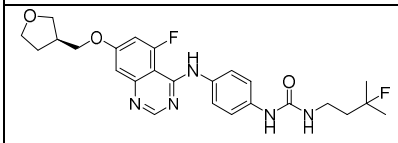
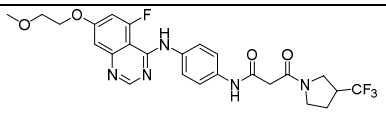
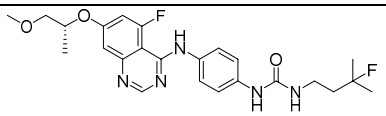
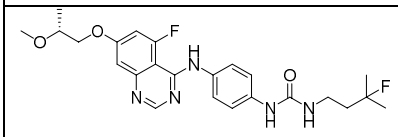
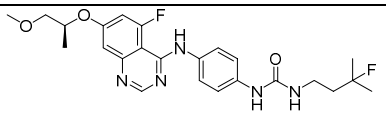
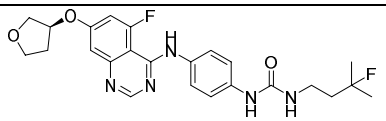
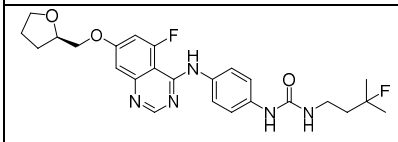
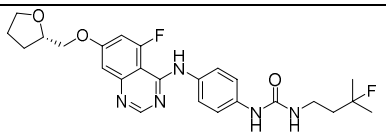
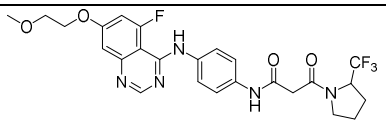
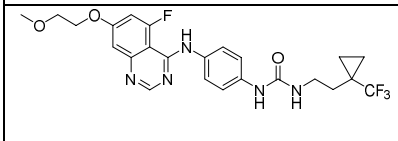
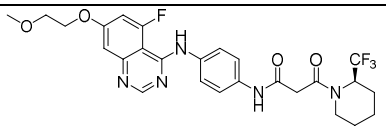
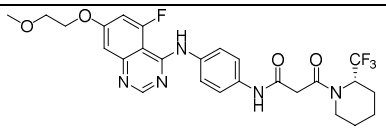
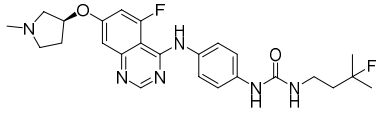
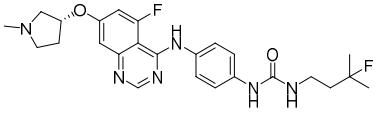
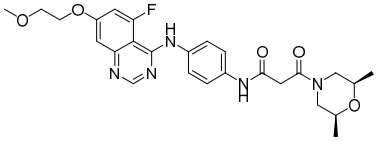
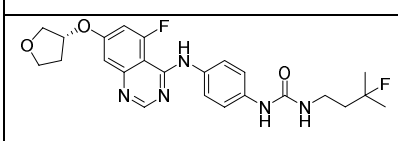
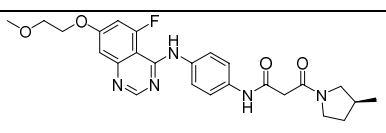
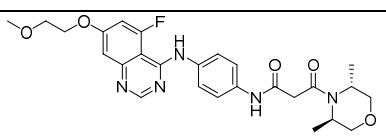
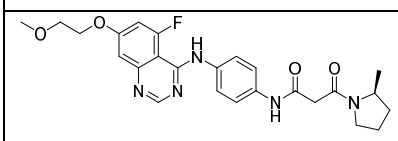
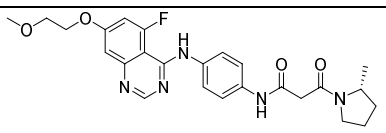
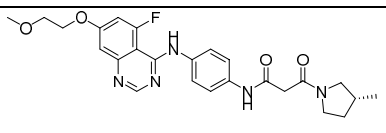
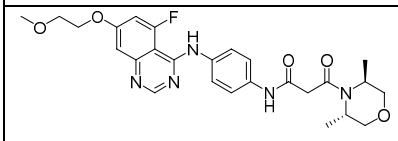
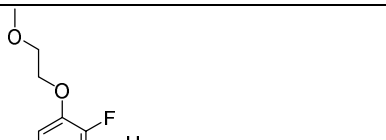
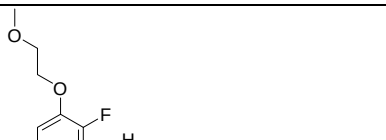
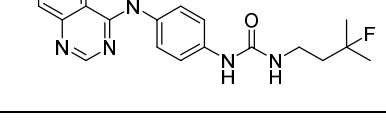
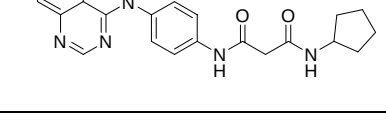
		
		
		
		
		
		
		
		
		
		
		
		
		

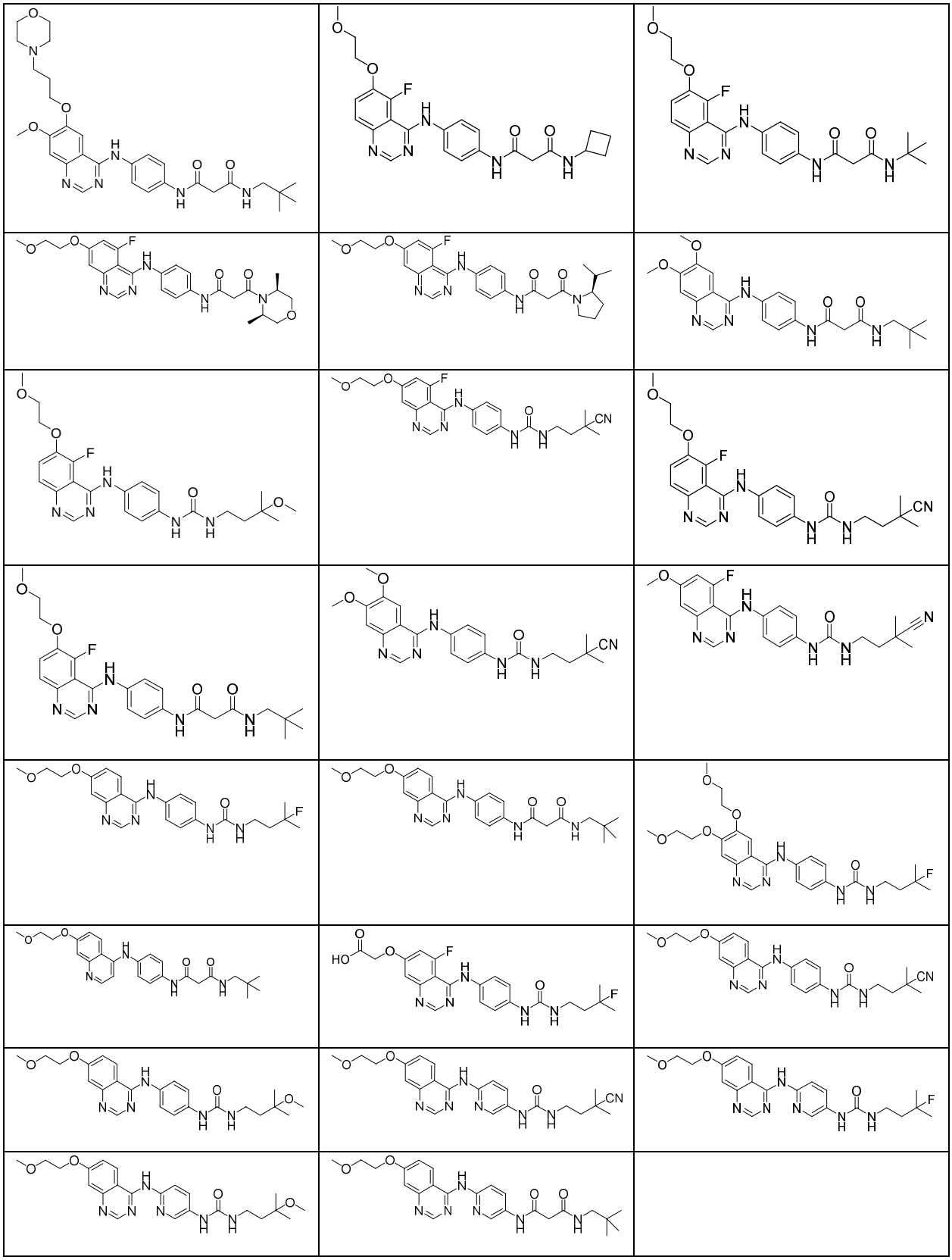
		
		
		
		
		
		
		
		
		
		
		
		
		





or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof.

[0008f] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient.

[0008g] In one aspect, the present disclosure refers to the compound disclosed herein, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, or the pharmaceutical composition disclosed herein, for use in treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT activated gastrointestinal stromal tumors, PDGFRa activated gastrointestinal stromal tumors (GIST), melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer in a patient in need thereof.

[0008h] In one aspect, the present disclosure refers to use of the compound disclosed herein, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT activated gastrointestinal stromal tumors, PDGFRa activated gastrointestinal stromal tumors (GIST), melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

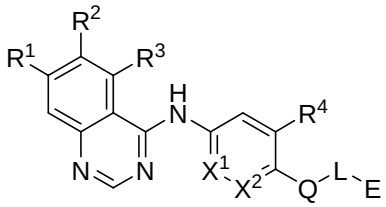
DETAILED DESCRIPTION

[0009] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula I-A:

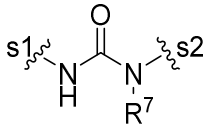
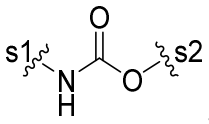


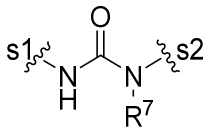
Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of

 , and  , wherein s1 is the site covalently linked to the ring; and s2 is the site covalently linked to L;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$, or when Q is  , L when taken together with R^7 and the N atom to which L and R^7 are attached form an optionally substituted heterocyclyl having from 4 to 10 atoms in the ring structure wherein the optional substituent is selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

E is selected from the group consisting of H, alkenyl, cyano, alkoxy, haloalkoxy, haloalkyl, halogen,

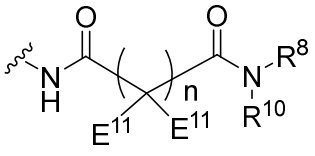
optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

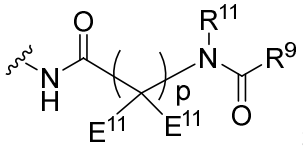
optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl; or

Q-L-E taken together is selected from the group consisting of



and


;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^1 is selected from the group consisting of H,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently, C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

optionally substituted cycloalkyloxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, amine, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

optionally substituted heterocyclyloxy wherein the optionally substituted substituent, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo, and

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkoxy, and hydroxy;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^1 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^7 is selected independently from the group consisting of H, alkyl, haloalkyl, or cycloalkyl;

R^8 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy,

amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{10} is selected from the group consisting of H and alkyl, or taken together with R^8 and the N atom to which R^8 and R^{10} are attached form an optionally substituted heterocyclyl having from 4 to 8 atoms in the ring structure wherein the optional substituent is, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

R^{11} is selected from the group consisting of H and alkyl, or taken together with R^9 and the atoms to which R^9 and R^{11} are respectively attached form an optionally substituted heterocyclyl having from 4 to 7 atoms in the ring structure wherein the optional substituent, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, and haloalkoxy;

each occurrence of m is independently 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

p is 1, 2, or 3; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

each cycloalkyl is C_3-C_{10} cycloalkyl;

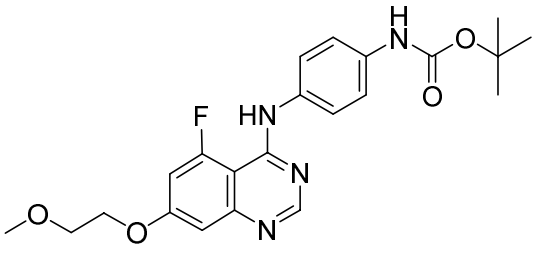
each cycloalkyloxy is C_3-C_6 cycloalkyloxy;

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose

ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms;

provided that the compound is not:



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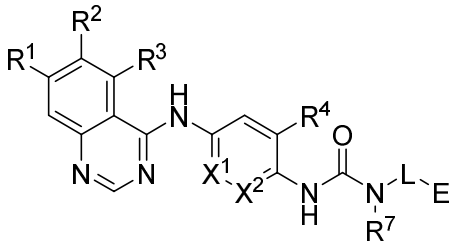
2. The compound of claim 1, which is:

a compound represented by Formula I-I:



Formula I-I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^7 and the N atom to which L and R^7 are attached form an optionally substituted heterocyclyl having from 4 to 10 atoms in the ring structure wherein the optional substituent is selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

E is selected from the group consisting of H, alkenyl, cyano, haloalkoxy, haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^1 is selected from the group consisting of H, haloalkyl,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently, C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

optionally substituted cycloalkyloxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of independently, C_1-C_6 alkyl, amine, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo, and

optionally substituted heterocyclyloxy wherein the optionally substituted substituent, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo, and

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkoxy, and hydroxy;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, alkoxy, amine, heterocyclyl, or when taken together with R^1 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

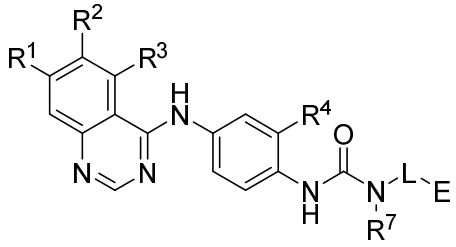
R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^7 is selected independently from the group consisting of H, alkyl, haloalkyl, or cycloalkyl; and

each occurrence of m is independently 0, 1, 2, 3, or 4; or

a compound represented by Formula I-J:



Formula I-J

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^7 and the N atom to which L and R^7 are attached form an optionally substituted heterocyclyl having from 4 to 10 atoms in the ring structure wherein the optional substituent is selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

E is selected from the group consisting of H, alkenyl, cyano, haloalkoxy, haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^1 is selected from the group consisting of H, haloalkyl,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently, C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

optionally substituted cycloalkyloxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of independently, C_1-C_6 alkyl, amine, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

optionally substituted heterocyclyloxy wherein the optionally substituted substituent, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo, and

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkoxy, and hydroxy;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, alkoxy, amine, heterocyclyl, or when taken together with R^1 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

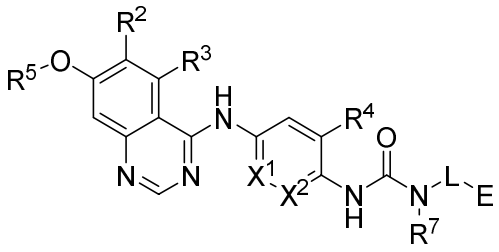
R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^7 is selected independently from the group consisting of H, alkyl, haloalkyl, or cycloalkyl; and

each occurrence of m is independently 0, 1, 2, 3, or 4; or

a compound represented by Formula I-K:



Formula I-K

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^7 and the N atom to which L and R^7 are attached form an optionally substituted heterocyclyl having from 4 to 10 atoms in the ring structure wherein the optional substituent is selected from

the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

E is selected from the group consisting of H, alkenyl, cyano, haloalkoxy, haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy,

acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen,

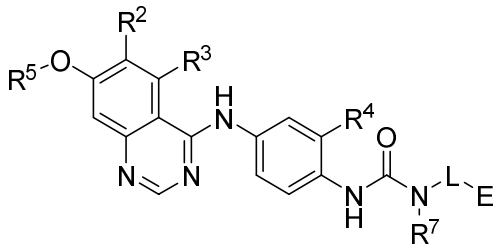
optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen;

R^7 is selected independently from the group consisting of H, alkyl, haloalkyl, or cycloalkyl; and

each occurrence of m is independently 0, 1, 2, 3, or 4; or

a compound represented by Formula I-L:



Formula I-L

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$, or when taken together with R^7 and the N atom to which L and R^7 are attached form an optionally substituted heterocyclyl having from 4 to 10 atoms in the ring structure wherein the optional substituent is selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo;

E is selected from the group consisting of H, alkenyl, cyano, haloalkoxy, haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl,

carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, and halogen,

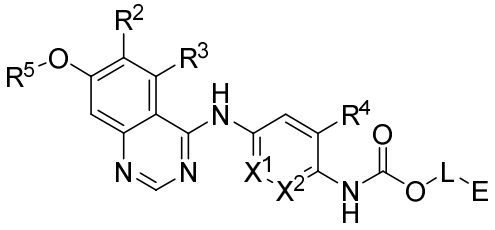
optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^7 is selected independently from the group consisting of H, alkyl, haloalkyl, or cycloalkyl; and

each occurrence of m is independently 0, 1, 2, 3, or 4; or

a compound represented by Formula I-O:



Formula I-O

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$;

E is selected from the group consisting of H, alkenyl, cyano, haloalkoxy, haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

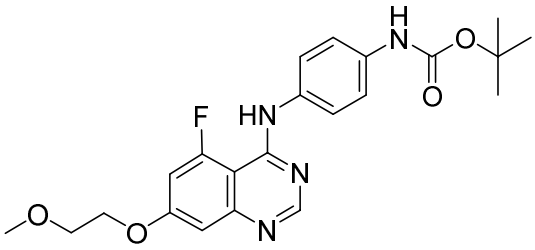
the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen; and

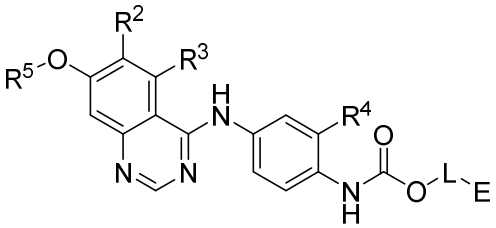
each occurrence of m is independently 0, 1, 2, 3, or 4;

provided that the compound is not:



; or

a compound represented by Formula I-Q:



Formula I-Q

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$;

E is selected from the group consisting of H, alkenyl, cyano, haloalkoxy, haloalkyl, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of cycloalkyl and heterocyclyl;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

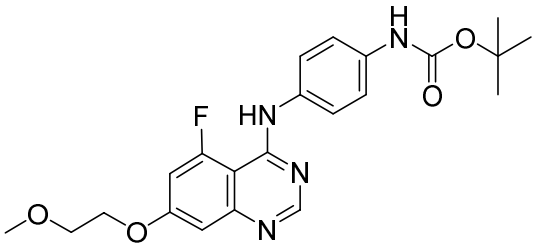
the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen; and

each occurrence of m is independently 0, 1, 2, 3, or 4,

provided that the compound is not:



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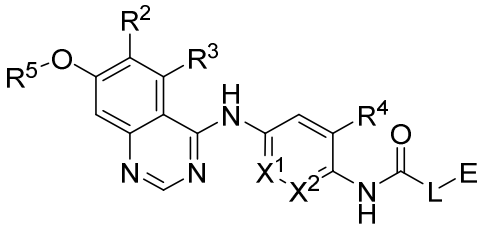
3. A compound

(i) represented by Formula I-T:



Formula I-T

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$;

E is selected from the group consisting of

optionally substituted amido wherein the substituent, at each occurrence, is independently, selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano,

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of cycloalkyl and heterocyclyl,

H, cyano, alkoxy, haloalkoxy, haloalkyl, and halogen;

E^{11}, at each occurrence, is independently, selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the

optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen; and

each occurrence of m is independently 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

each cycloalkyl is C_3-C_{10} cycloalkyl;

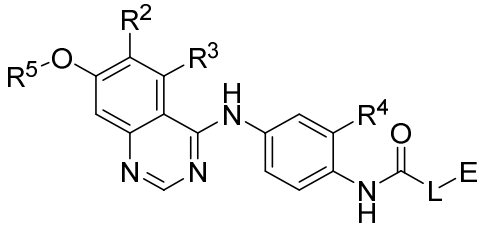
each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose

ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms; or

(ii) represented by Formula I-U:



Formula I-U

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

L is selected from the group consisting of a direct bond and a C_1-C_6 alkyl optionally substituted with $(E^{11})_m$;

E is selected from the group consisting of

optionally substituted amido wherein the substituent, at each occurrence, is independently, selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano,

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of cycloalkyl, heterocyclyl,

H, cyano, alkoxy, haloalkoxy, haloalkyl, and halogen;

E^{11}, at each occurrence, is independently, selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of F and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen; and

each occurrence of m is independently 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

each cycloalkyl is C_3-C_{10} cycloalkyl;

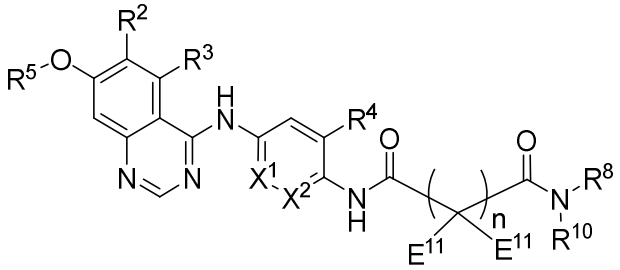
each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms.

4. A compound

(i) represented by Formula I-X:



Formula I-X

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen;

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^8 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{10} is selected from the group consisting of H and alkyl, or taken together with R^8 and the N atom to which R^8 and R^{10} are attached form an optionally substituted heterocyclyl having from 4 to 8 atoms in the ring structure wherein the optional substituent is, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo; and

n is 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

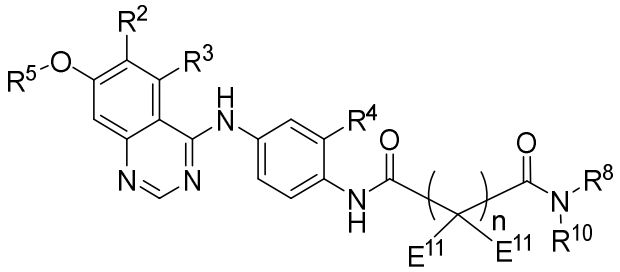
each cycloalkyl is C_3-C_{10} cycloalkyl;

each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

wherein each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms; or

(ii) represented by Formula I-Y:



Formula I-Y

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen;

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^8 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{10} is selected from the group consisting of H and alkyl, or taken together with R^8 and the N atom to which R^8 and R^{10} are attached form an optionally substituted heterocyclyl having from 4 to 8 atoms in the ring structure wherein the optional substituent is, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, haloalkoxy, and oxo; and

n is 0, 1, 2, 3, or 4; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

each cycloalkyl is C_3-C_{10} cycloalkyl;

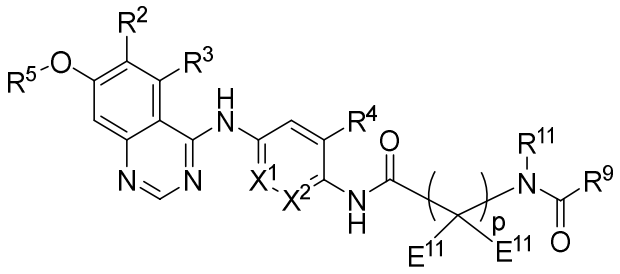
each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms.

5. A compound

(i) represented by Formula I-AB:



Formula I-AB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^2 are each independently selected from the group consisting of N, CH, and CF;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{11} is selected from the group consisting of H and alkyl, or taken together with R^9 and the atoms to which R^9 and R^{11} are respectively attached form an optionally substituted heterocyclyl having from 4 to 7 atoms in the ring structure wherein the optional substituent, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, and haloalkoxy; and

p is 1, 2, or 3; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

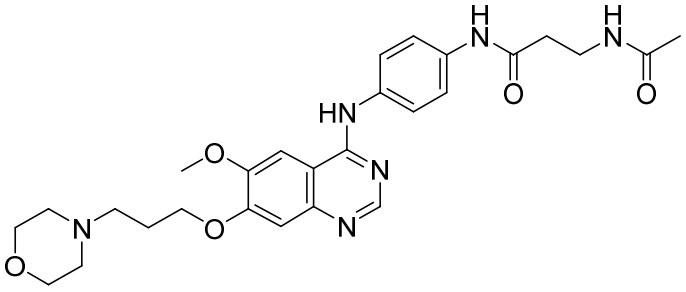
each cycloalkyl is C_3-C_{10} cycloalkyl;

each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

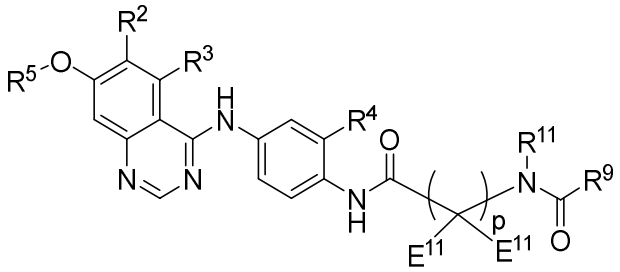
each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms;

provided that the compound is not:



; or

(ii) represented by Formula I-AC:



Formula I-AC

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen, or two occurrences of E^{11} when taken together with the C atom to which they are attached form an optionally substituted cycloalkyl having from 3 to 4 atoms in the ring structure, wherein the optional substituent is selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo;

R^2 is selected from the group consisting of H and optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently alkoxy, amine, heterocyclyl, or when taken together with R^5 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

R^3 is selected from the group consisting of H, F, and alkoxy;

R^4 is selected from the group consisting of H, F, alkyl, and alkoxy;

R^5 is selected from the group consisting of

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, oxo, and halogen,

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, oxo, and halogen, and

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, wherein

the substituent of the optionally substituted alkyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy,

amine, halogen, haloalkyl, haloalkoxy, hydroxy, cyano, cycloalkyl, and heterocyclyl,

the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, oxo, and cyano, and

the substituent of the optionally substituted cycloalkyl at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano;

R^{11} is selected from the group consisting of H and alkyl, or taken together with R^9 and the atoms to which R^9 and R^{11} are respectively attached form an optionally substituted heterocyclyl having from 4 to 7 atoms in the ring structure wherein the optional substituent, at each occurrence, is independently selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyl, alkoxy, and haloalkoxy; and

p is 1, 2, or 3; wherein

each heterocyclyl is 3- to 10-membered heterocyclyl comprising one to four heteroatoms;

each alkyl is C_1-C_6 alkyl;

each alkoxy is C_1-C_6 alkoxy;

each alkenyl is C_2-C_8 alkenyl;

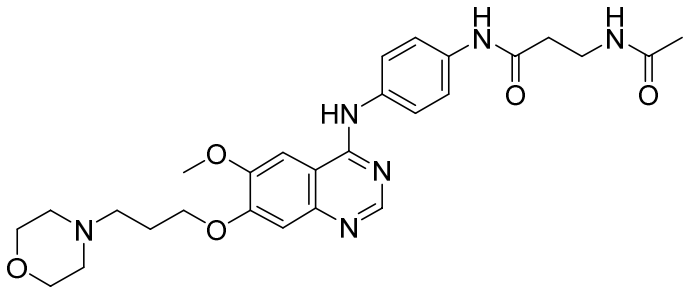
each cycloalkyl is C_3-C_{10} cycloalkyl;

each cycloalkyloxy is C_3-C_6 cycloalkyloxy; and

each heterocyclyloxy is 3- to 10-membered heterocyclyloxy comprising one to four heteroatoms;

each heterocyclyl independently is a substituted or unsubstituted non-aromatic ring structure, including monocyclic, polycyclic bridged, or fused ring structure, optionally a 3- to 10-membered ring, or optionally a 3- to 7-membered ring, whose ring structure includes at least one heteroatom, optionally one to four heteroatoms, optionally one or two heteroatoms;

provided that the compound is not:



.

6. The compound of claim 1, wherein R^1 is selected from the group consisting of H, haloalkyl,

optionally substituted C_1-C_6 alkoxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, carboxylic acid, optionally substituted amido, and optionally substituted heterocyclyl, wherein

the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl,

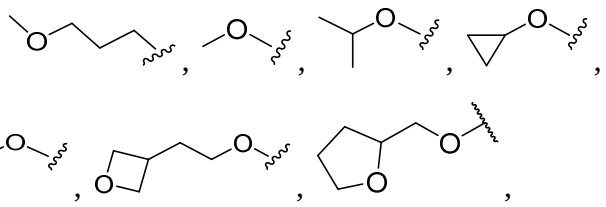
the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently C_1-C_6 alkyl, amine, cyano, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo,

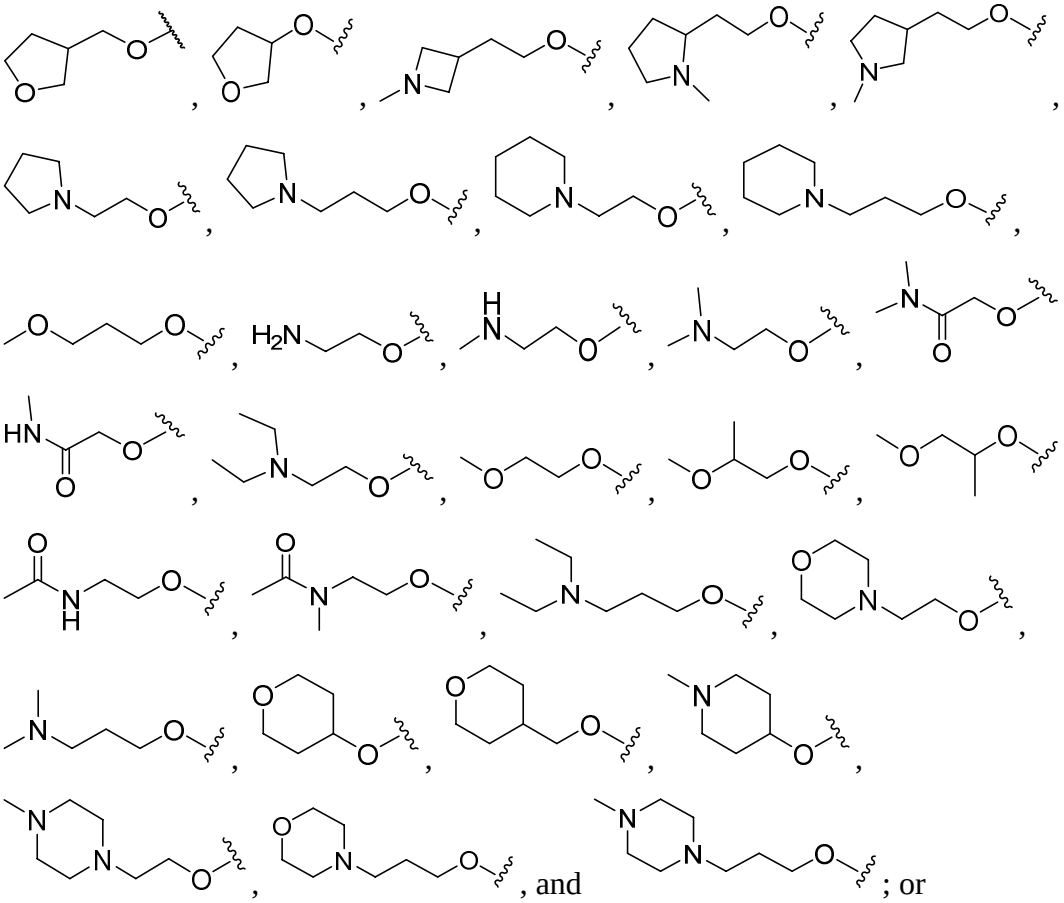
optionally substituted C_4-C_6 cycloalkyloxy wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of independently, C_1-C_6 alkyl, amine, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, hydroxy, and oxo, and

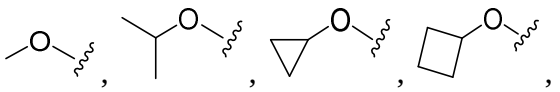
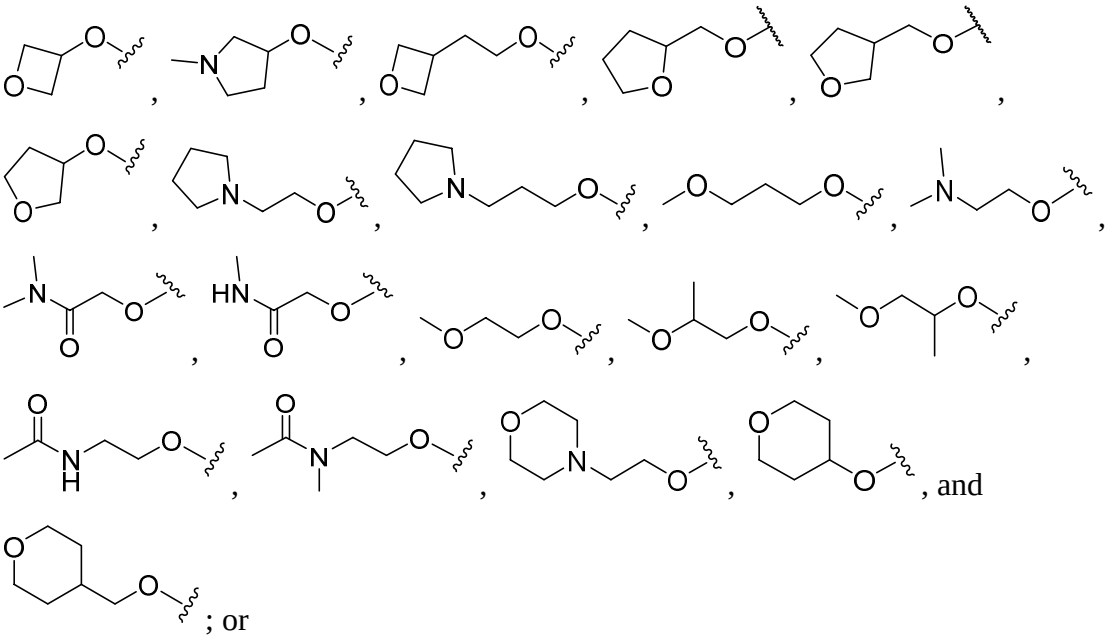
optionally substituted C_1-C_6 alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, amine, haloalkoxy, and hydroxy.

7. The compound of any one of claims 1-2 and 6, wherein:

(i) (a) R^1 is selected from

the group consisting of H, 


, and ; or

the group consisting of H, 

, and

; or

(b) R^5 is selected from the group consisting of:

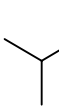
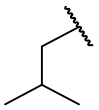
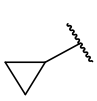
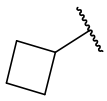
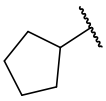
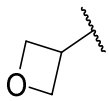
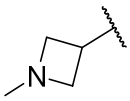
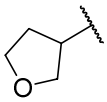
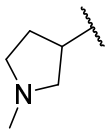
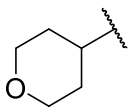
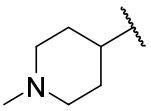
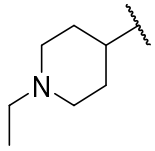
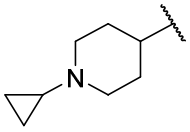
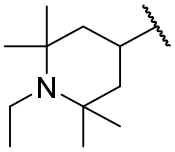
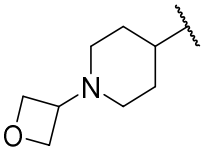
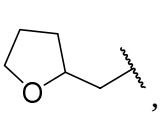
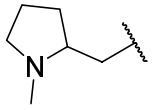
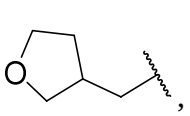
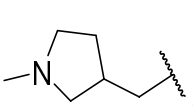
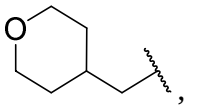
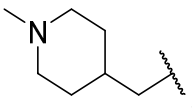
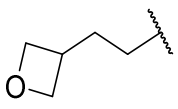
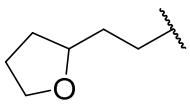
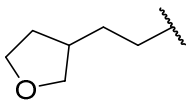
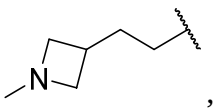
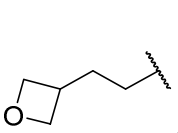
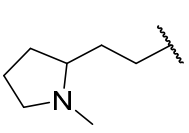
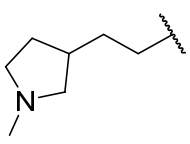
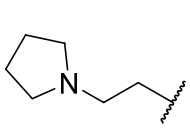
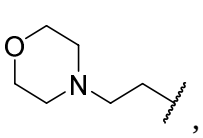
optionally substituted C_1-C_6 alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkoxy, acetamido, amine, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, cycloalkyl, optionally substituted amido, and optionally substituted heterocyclyl, wherein

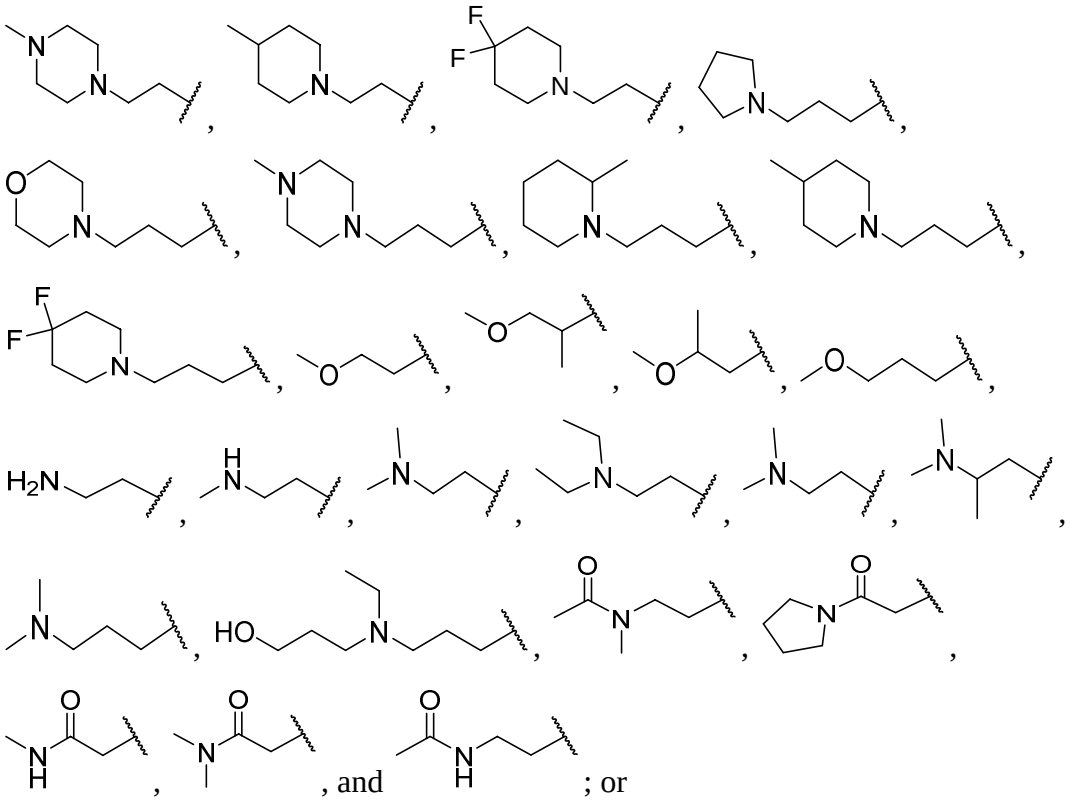
the substituent of the optionally substituted amido, at each occurrence, is independently C_1-C_6 alkyl, and

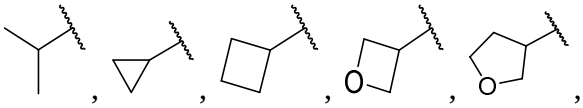
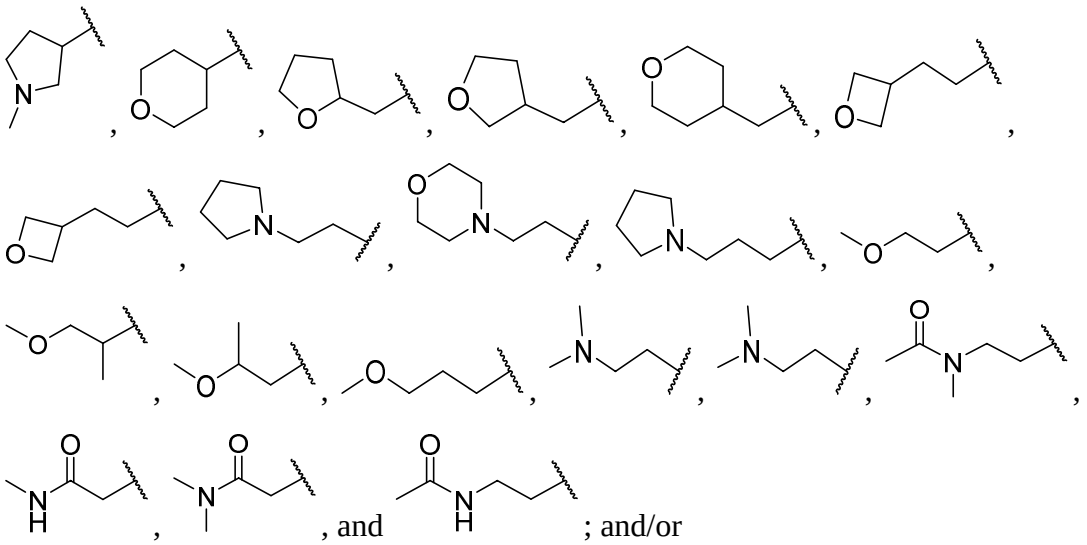
the substituent of the optionally substituted heterocyclyl, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, and halogen,

optionally substituted C_1-C_6 heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen; and

optionally substituted C_1-C_6 cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, and halogen;

the group consisting of methyl, ethyl, CF_3, CHF_2, CH_2CF_3,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

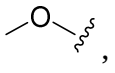
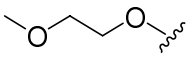
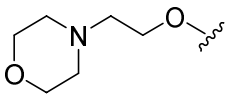

, and ; or

the group consisting of methyl, 

, and ; and/or

(ii) R^2 is:

selected from the group consisting of H, and optionally substituted C_1-C_6 alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, alkoxy, amine, heterocyclyl, or when taken together with R^1 form an optionally substituted heterocyclyl having from 5 to 6 atoms in the ring structure

wherein the optionally substituted substituent, at each occurrence, is independently selecting from the group consisting of C_1-C_6 alkyl and halogen;

selected from the group consisting of H,  ,  , and  ; or

is H.

8. The compound of any one of claims 1-7, wherein:

R^3 is F; and/or

R^4 is selected from the group consisting of H, F, C_1-C_6 alkyl, and alkoxy; and/or

R^4 is H; and/or

X^1, X^2, X^3, and X^4 are independently CH or N, provided that not more that one of X^3 and X^4 is N; and/or

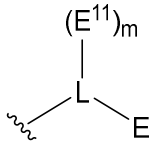
X^1 is CH and X^2 is CH; and/or

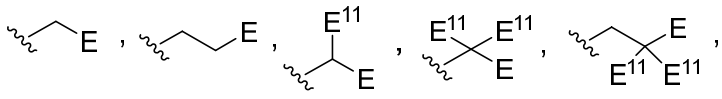
X^1 is CH and X^2 is N; and/or

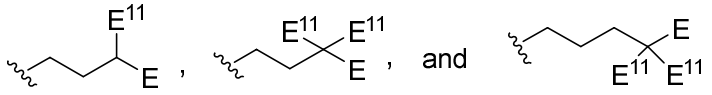
X^3 is CH and X^4 is N.

9. The compound of any one of claims 1-2 and 4-8, wherein L is selected from the group consisting of direct bond and C_1-C_6 alkyl optionally substituted with $(E^{11})_m$.

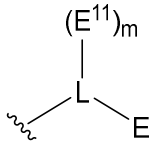
10. The compound of any one of claims 1-3 and 6-9, wherein:

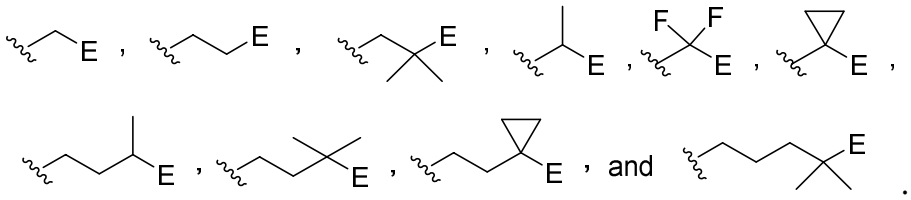
(i)  is selected from the group consisting of



 ; and/or E^{11}, at each occurrence, is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_5 cycloalkyl,

and halogen, for example, wherein E^{11}, at each occurrence, is independently selected from the group consisting of H, methyl, and fluoro; or

(ii)  is selected from the group consisting of



11. The compound of any one of claims 1-3 and 6-10, wherein E is selected from:

(i) the group consisting of H, C_1-C_6 alkenyl, cyano, haloalkoxy, haloalkyl, halogen,

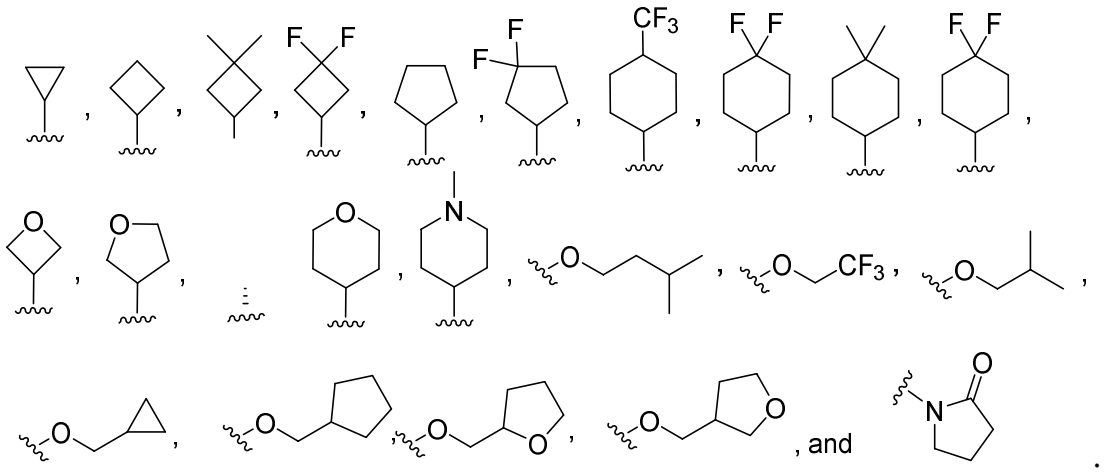
optionally substituted C_1-C_6 alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

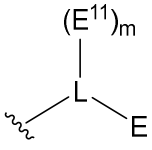
optionally substituted C_3-C_6 cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amine, halogen, haloalkyl, haloalkoxy, hydroxy, and cyano,

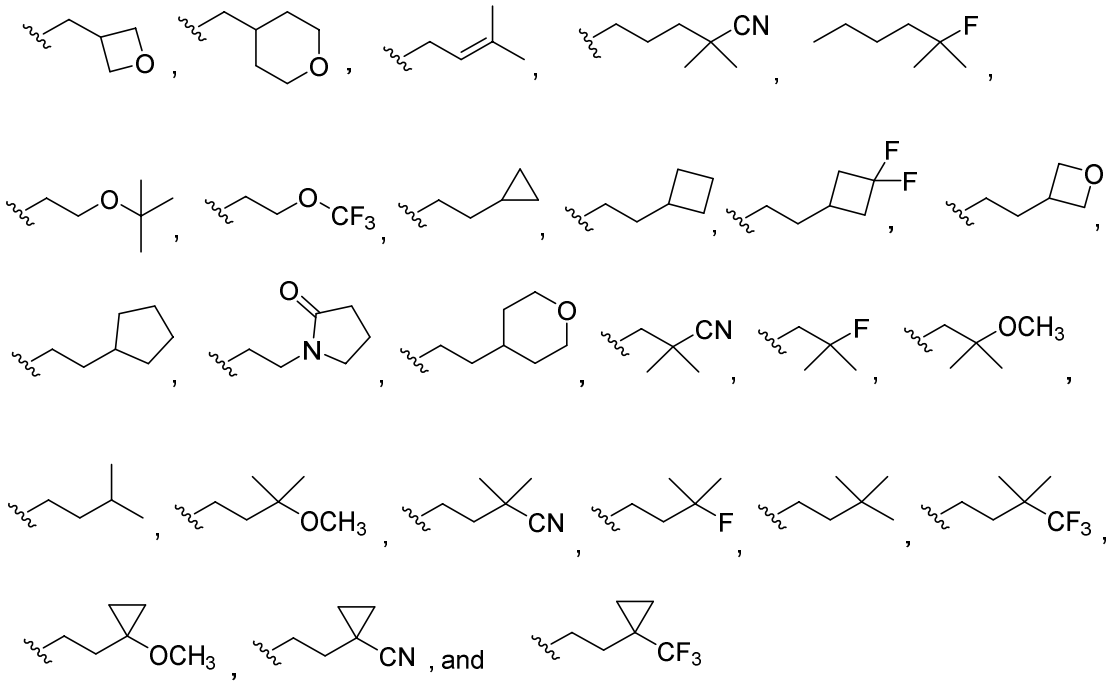
optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of C_1-C_6 alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone; and

optionally substituted alkoxy wherein the optionally substituted substituent, at each occurrence, is independently, selected from the group consisting of cycloalkyl, and heterocyclyl; or

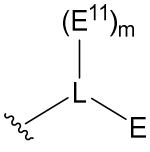
(ii) the group consisting of H, fluoro, methyl, trifluoromethyl, methoxy, *tert*-butoxy, trifluoromethoxy, cyano, alkenyl,

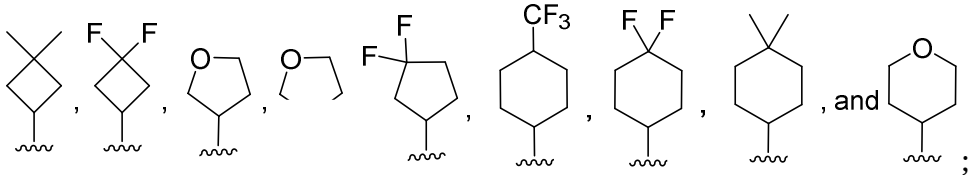


12. The compound of any one of claims 1-11, wherein  is selected from the group consisting of



; or

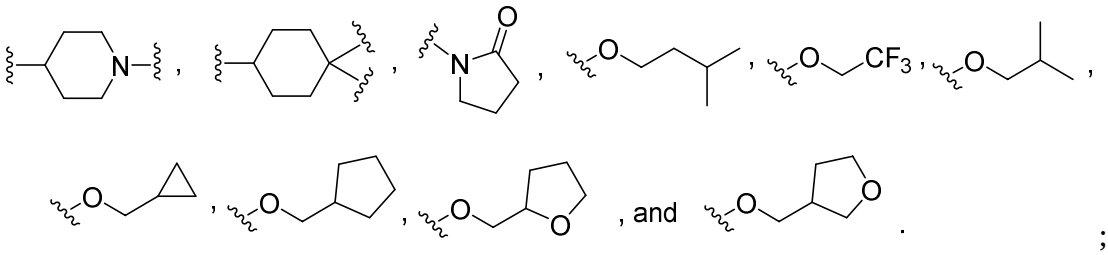
wherein when L is a direct bond,  is selected from the group consisting of

 ; and/or

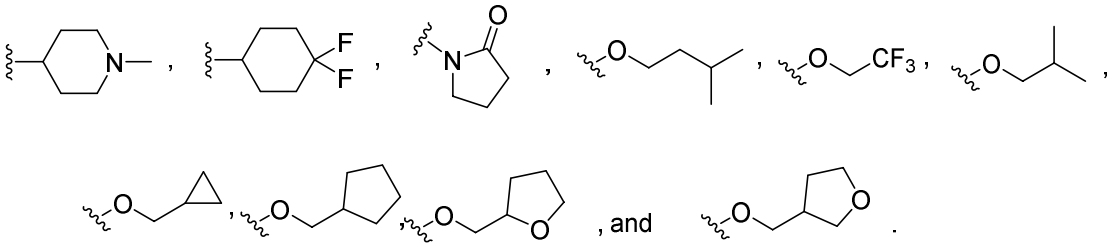
wherein R^7 is H, alkyl, or haloalkyl, for example R^7 is H.

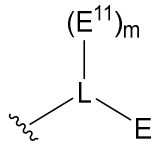
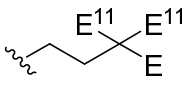
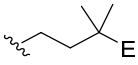
13. The compound of any one of claims 1-2, and 6-9, wherein:

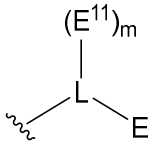
(i) E is selected from the group consisting of H, fluoro, methoxy, and cyano; the group consisting of H, fluoro, methyl, trifluoromethyl, methoxy, cyano;

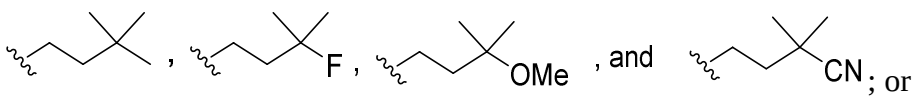
 ;

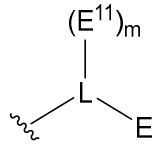
or the group consisting of H, fluoro, methyl, trifluoromethyl, methoxy, cyano,

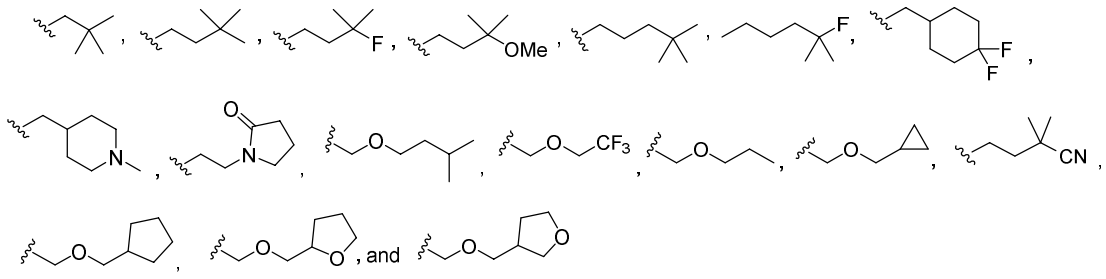
 ; or

(ii)  is  , for example  , such as wherein

 is selected from the group consisting of

 ; or

(iii)  is selected from the group consisting of



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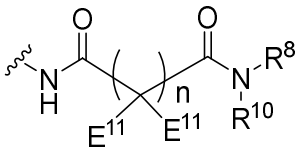
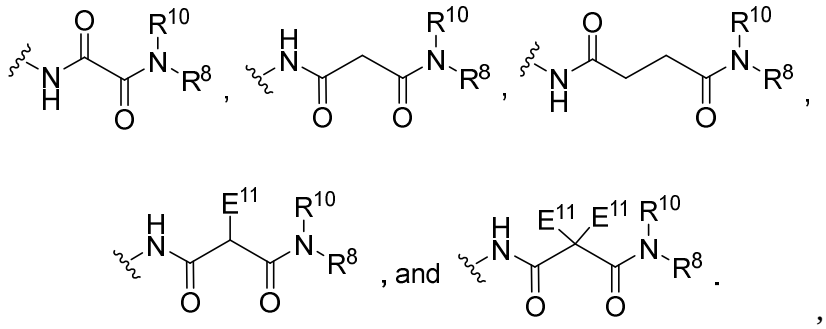
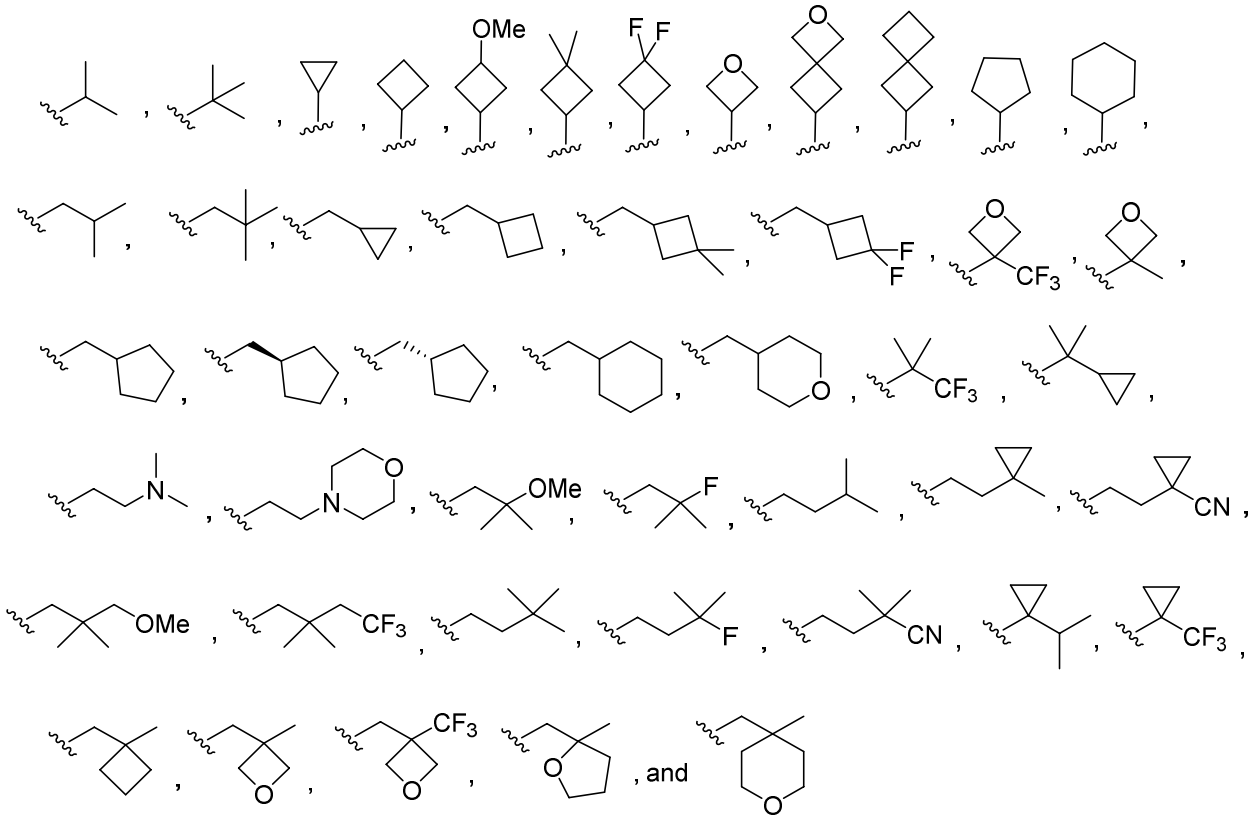
14. The compound of any one of claims 1, 2 and 5, wherein  is selected from the group consisting of

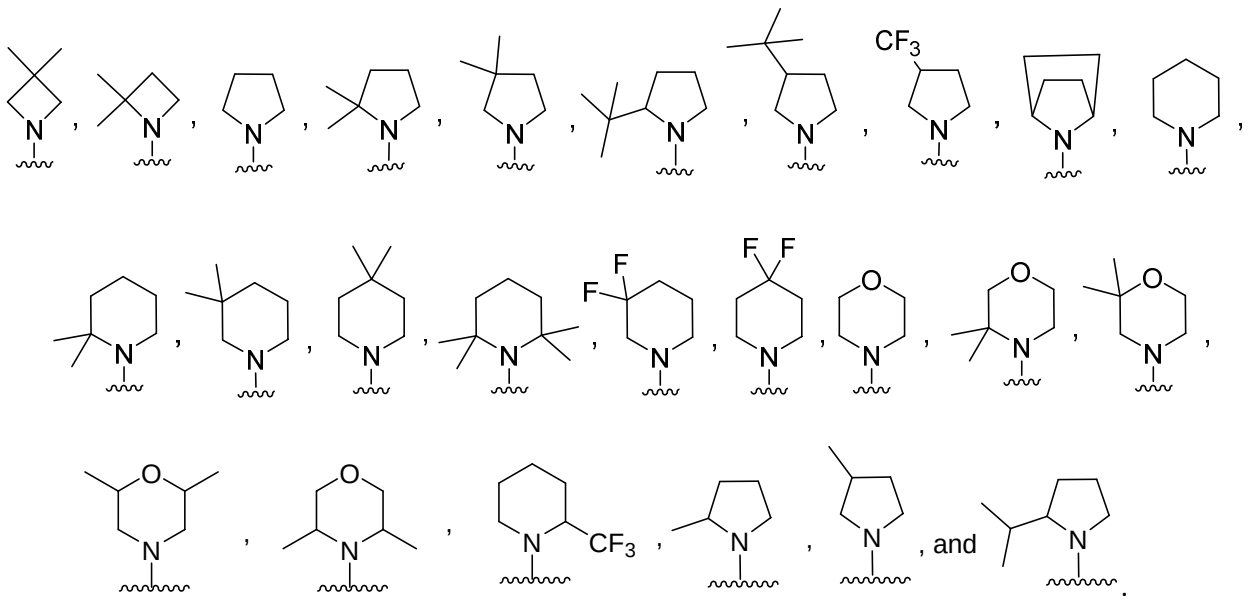


optionally wherein E^{11}, at each occurrence, is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, and halogen, for example the group consisting of H, methyl, and fluoro.

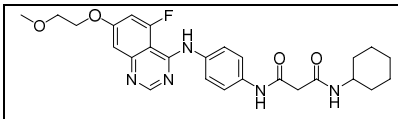
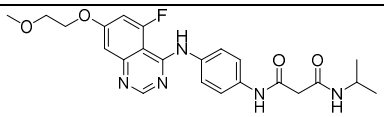
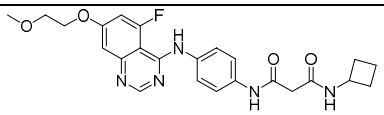
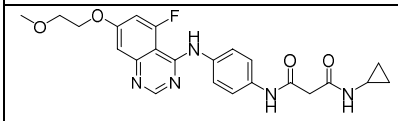
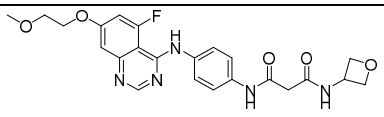
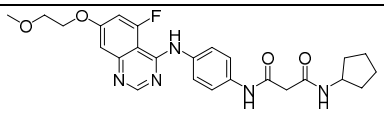
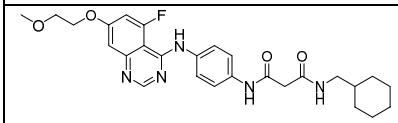
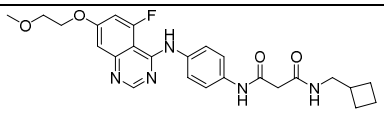
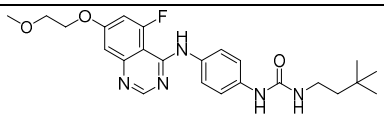
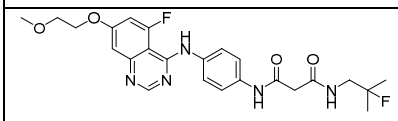
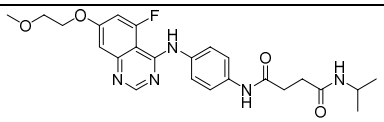
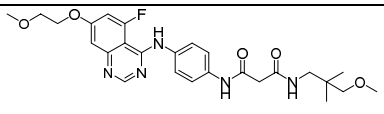
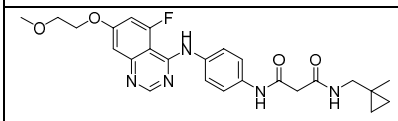
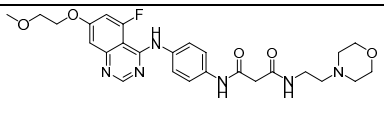
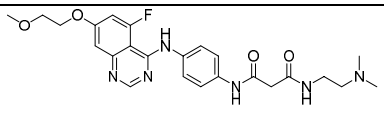
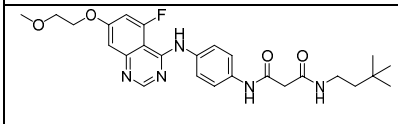
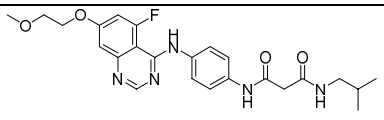
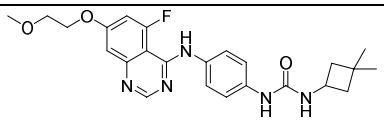
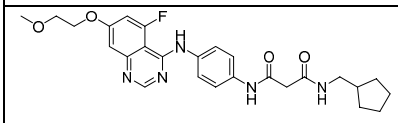
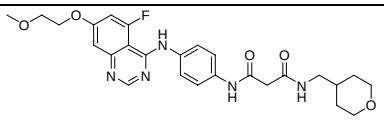
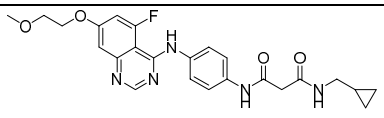
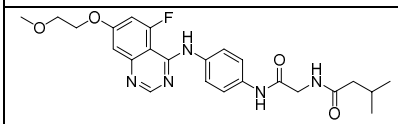
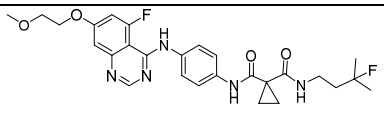
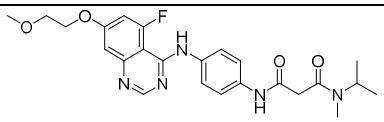
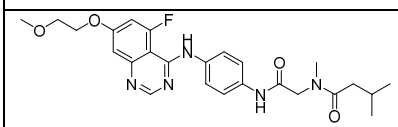
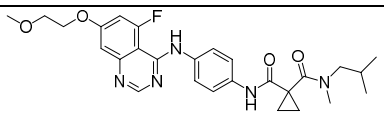
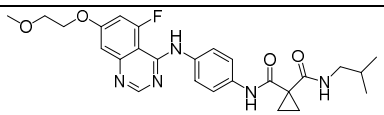
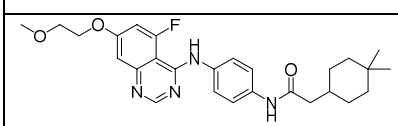
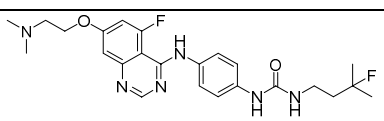
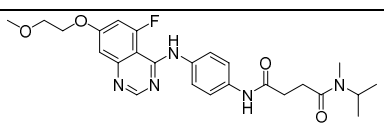
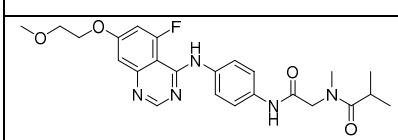
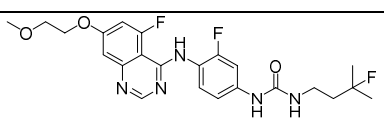
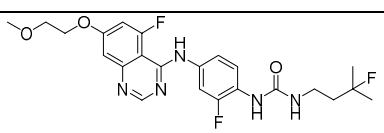
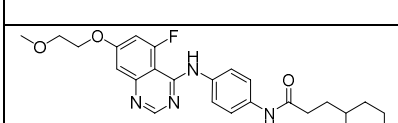
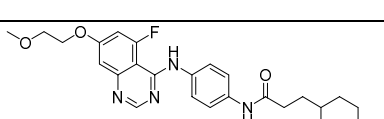
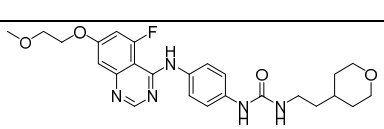
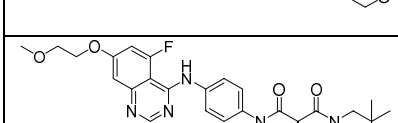
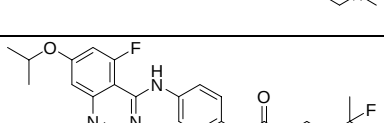
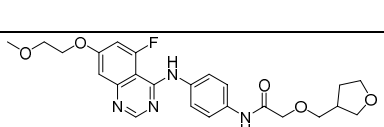
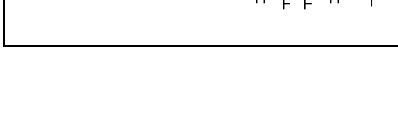
15. The compound of any one of claims 1, 2, 5-10, or 14, wherein R^8 is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl, and R^{10} is selected from the group consisting of H and alkyl; or wherein R^8 is selected from the group consisting of

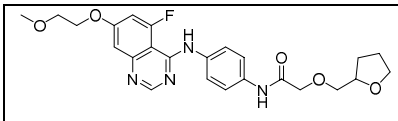
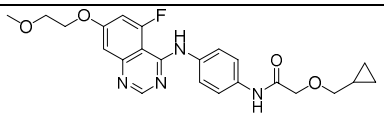
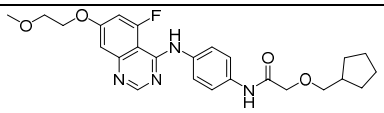
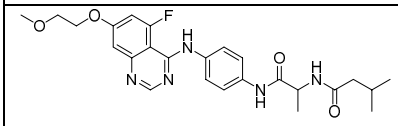
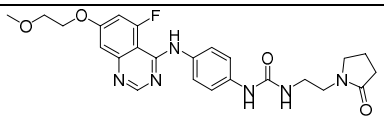
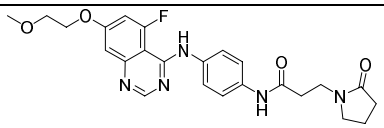
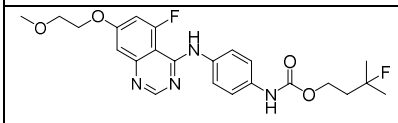
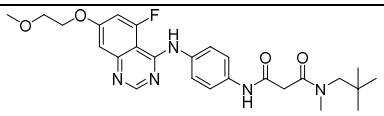
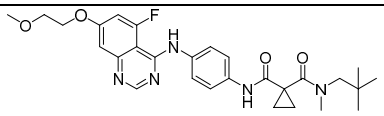
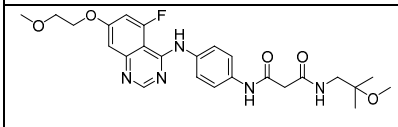
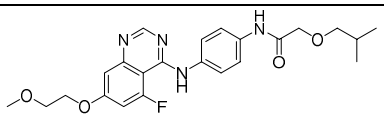
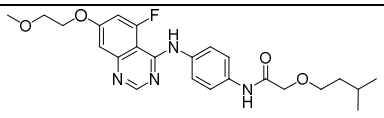
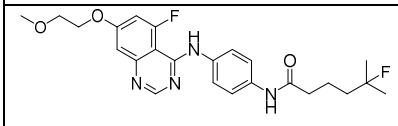
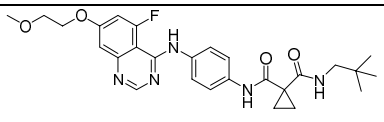
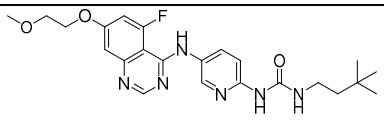
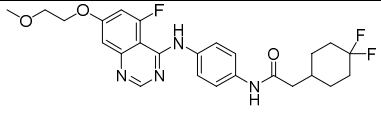
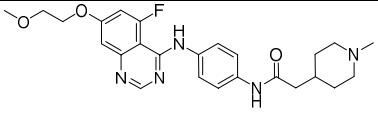
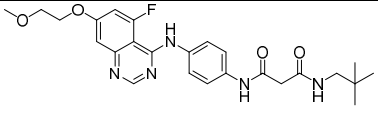
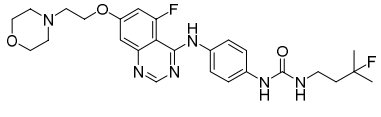
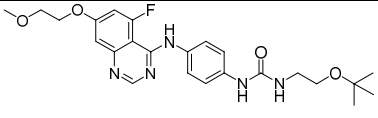
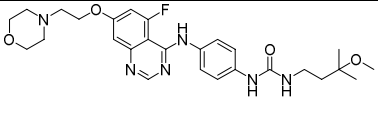
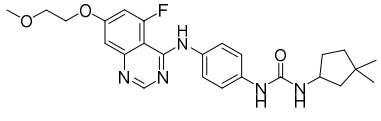
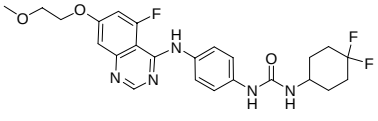
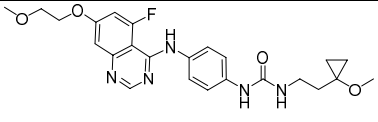
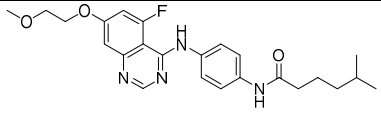
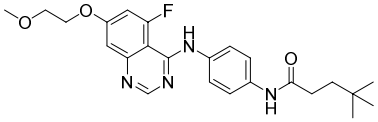
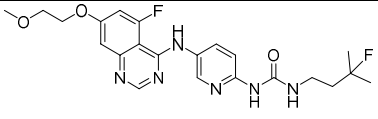
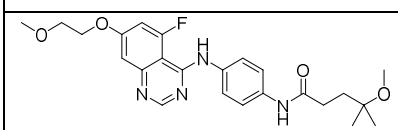
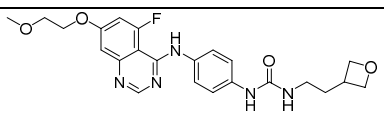
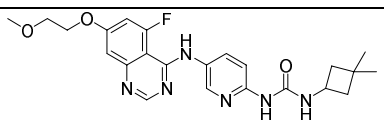
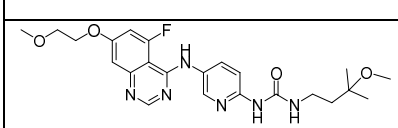
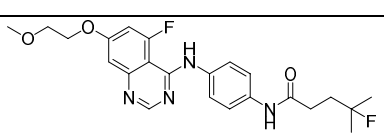
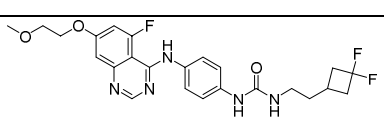
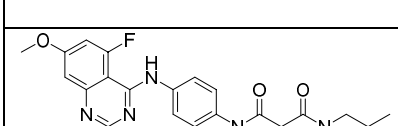
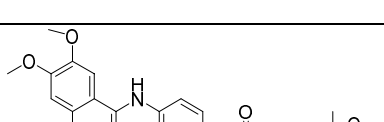
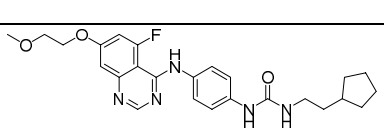
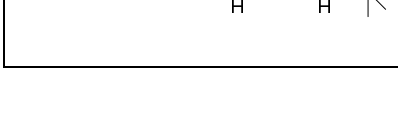
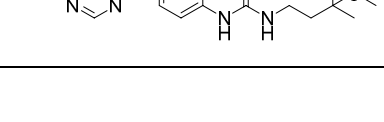


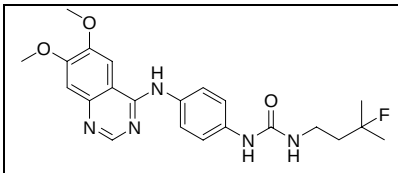
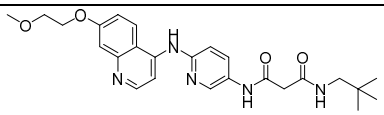
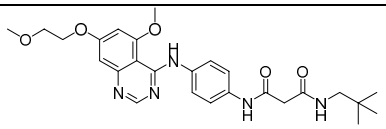
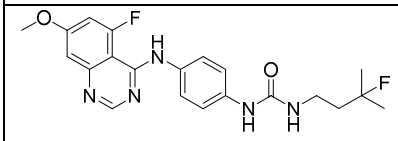
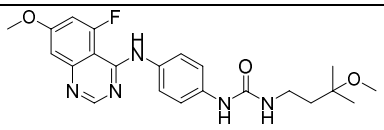
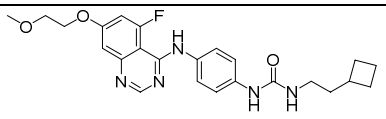
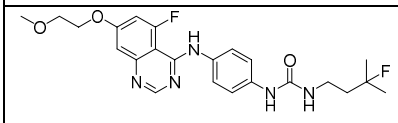
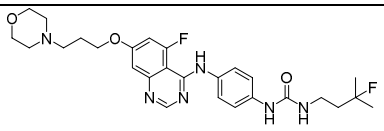
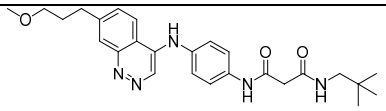
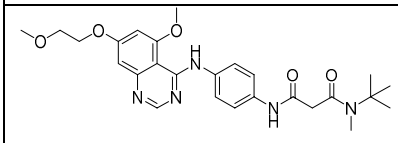
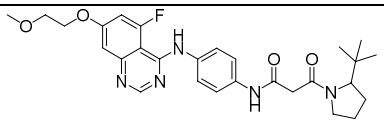
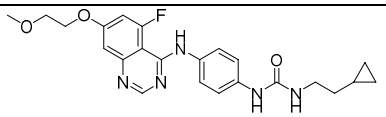
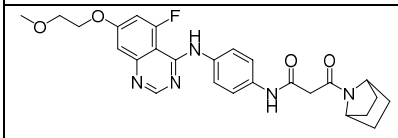
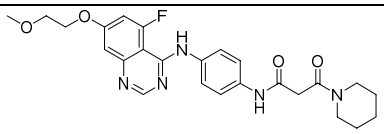
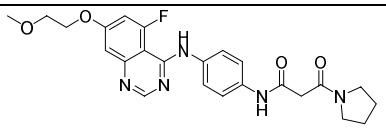
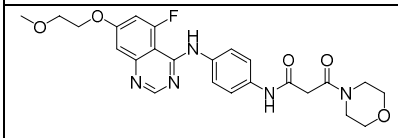
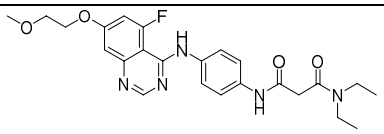
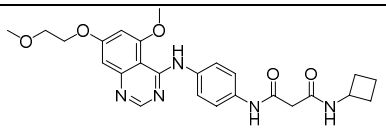
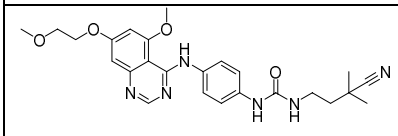
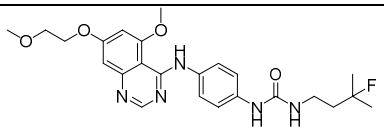
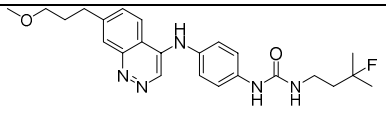
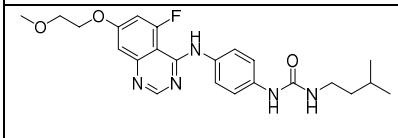
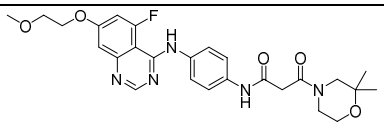
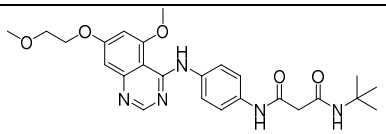
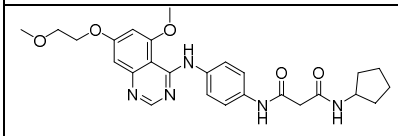
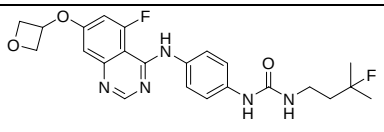
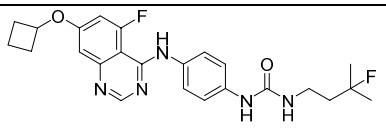
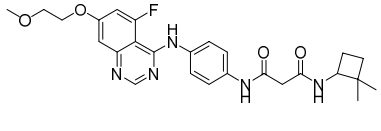
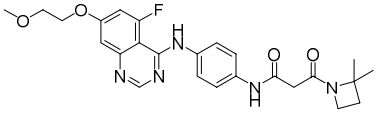
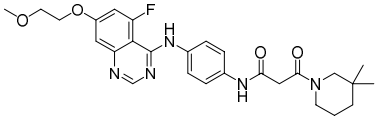
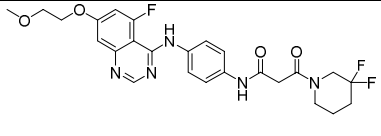
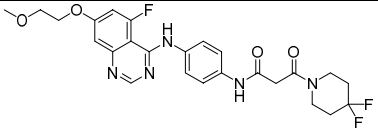
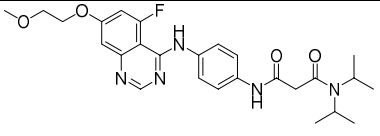
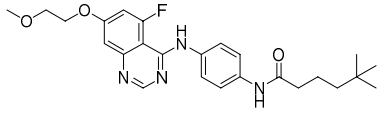
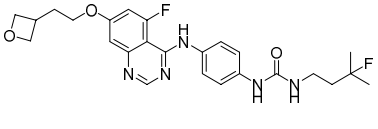
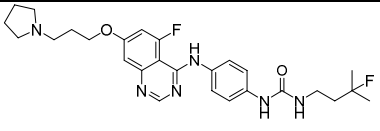
, and R^{10} is selected from the group consisting of H, methyl, ethyl, and isopropyl; or wherein R^8 taken together with R^{10} and the N atom to which R^8 and R^{10} are attached form a ring structure selected from the group consisting of

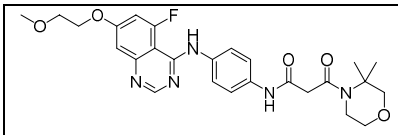
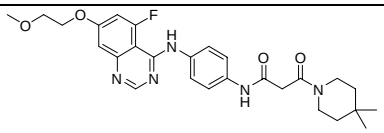
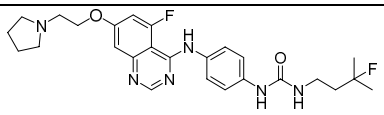
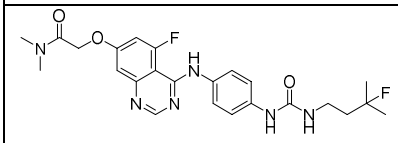
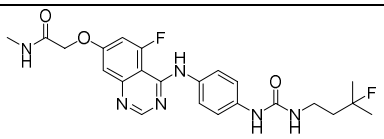
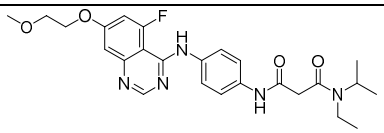
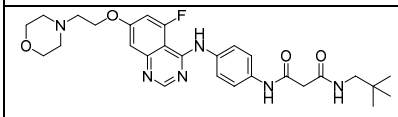
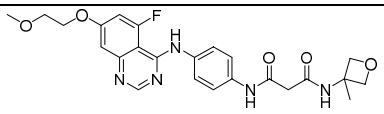
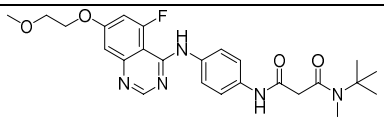
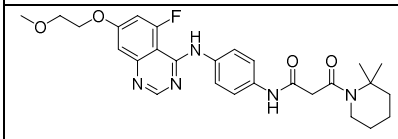
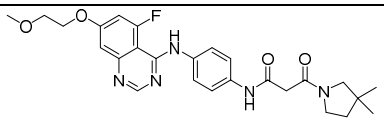
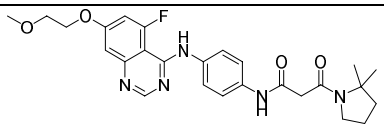
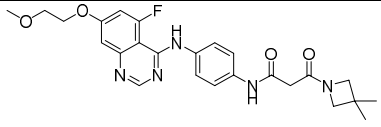
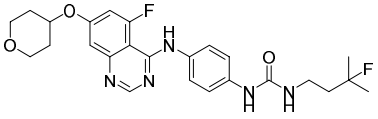
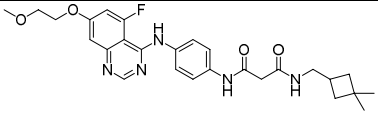
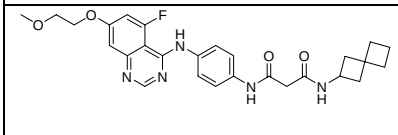
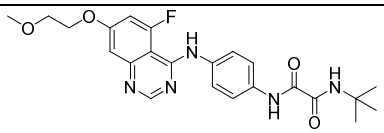
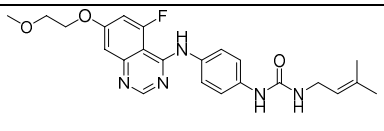
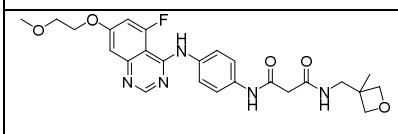
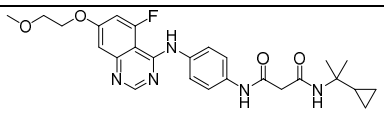
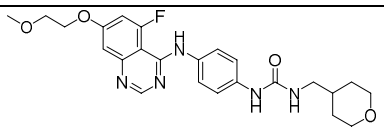
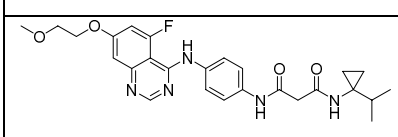
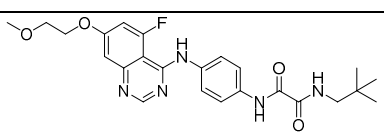
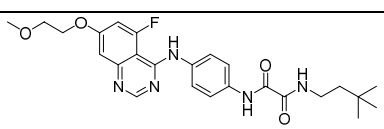
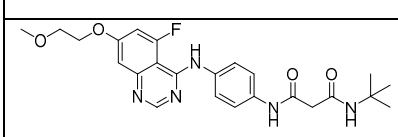
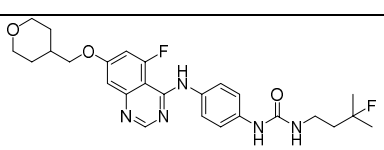
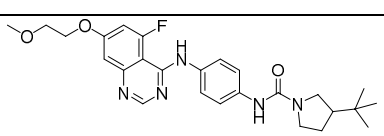
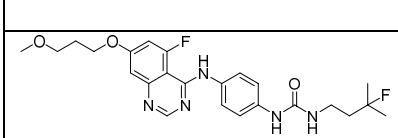
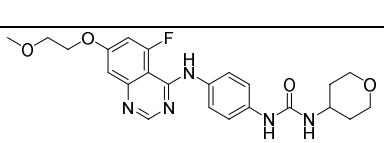
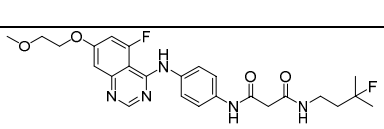
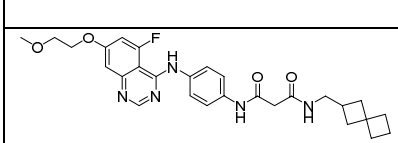
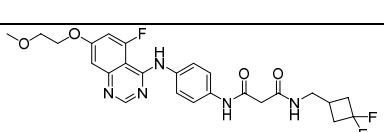
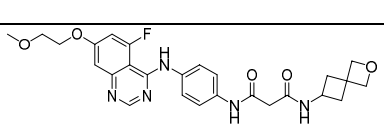
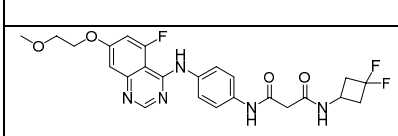
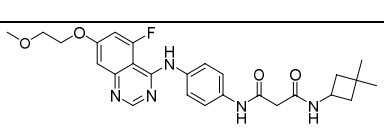
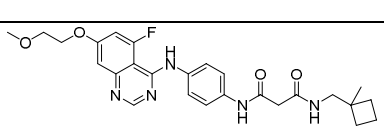


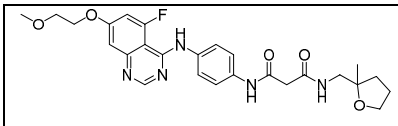
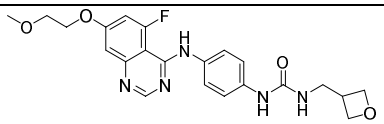
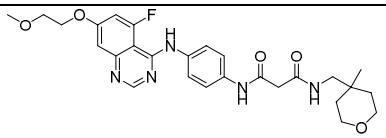
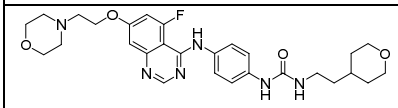
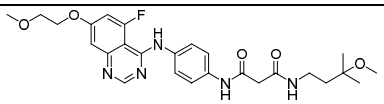
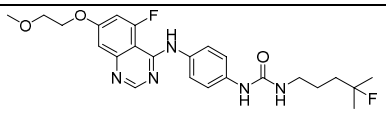
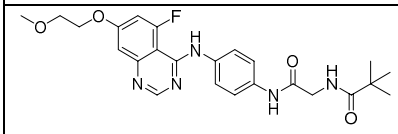
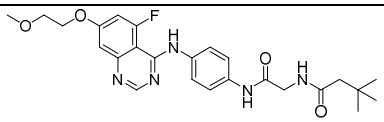
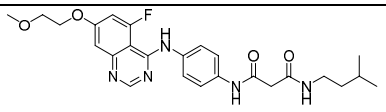
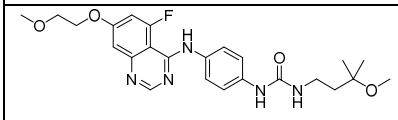
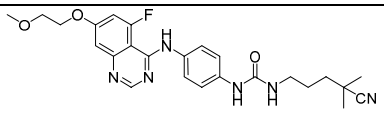
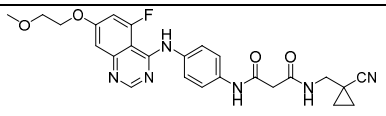
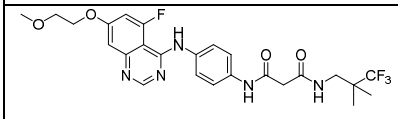
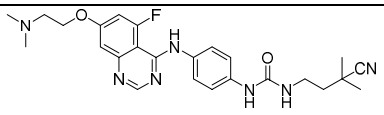
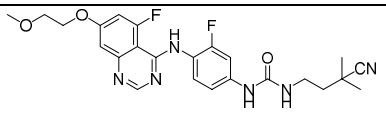
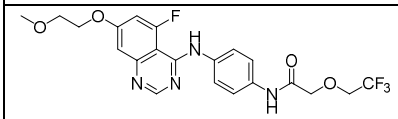
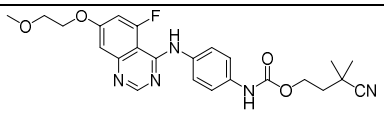
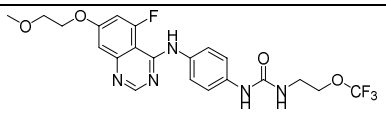
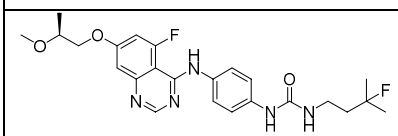
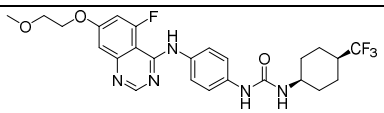
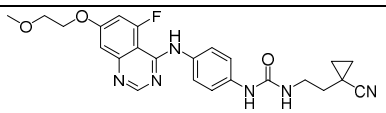
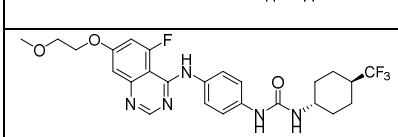
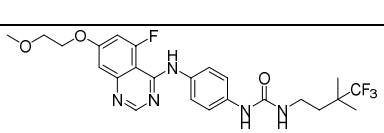
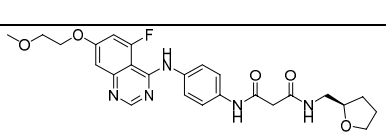
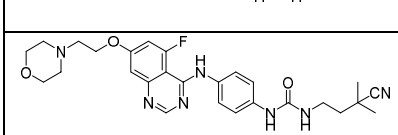
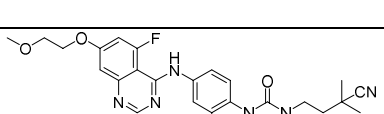
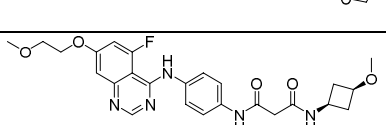
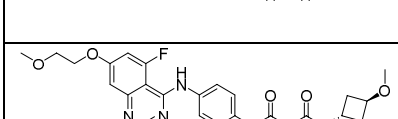
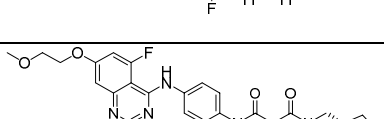
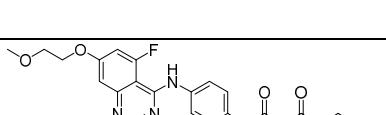
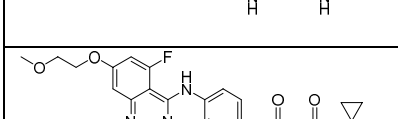
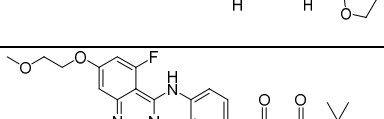
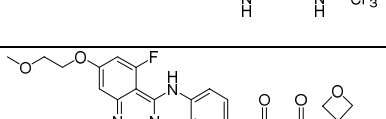
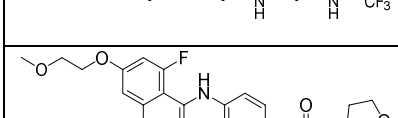
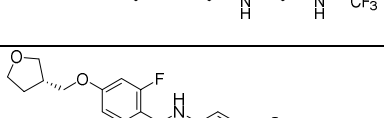
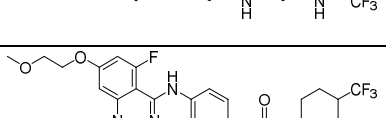
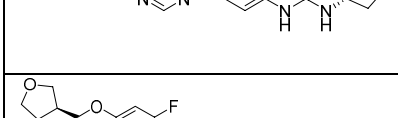
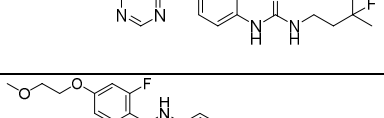
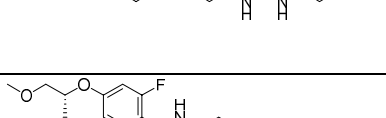
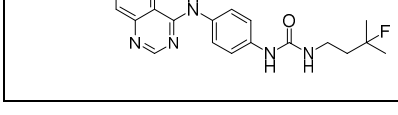
16. A compound selected from:

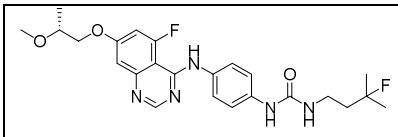
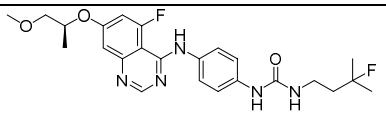
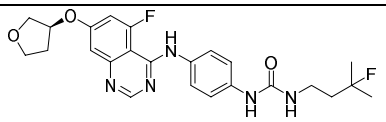
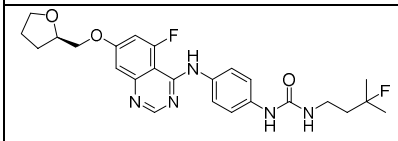
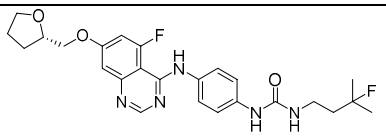
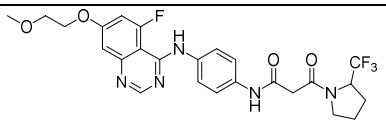
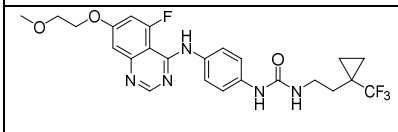
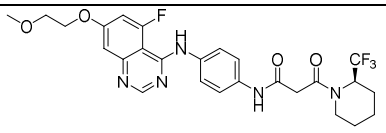
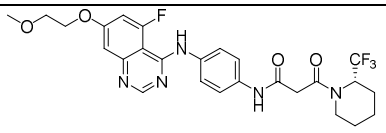
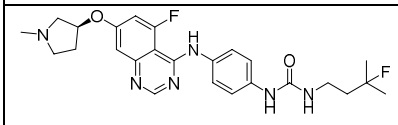
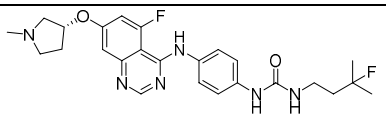
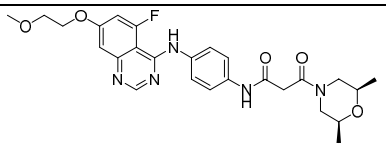
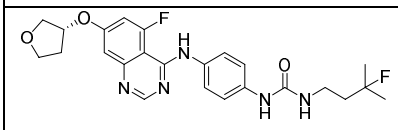
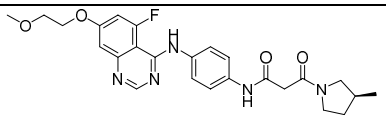
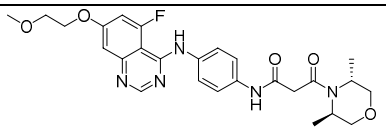
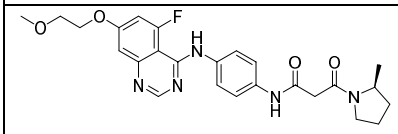
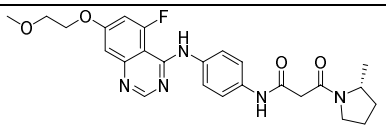
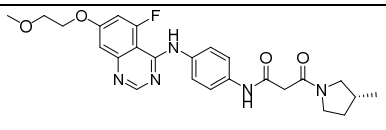
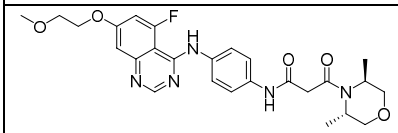
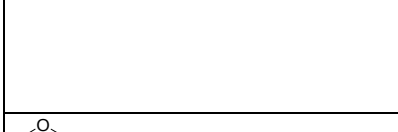
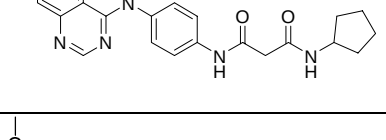
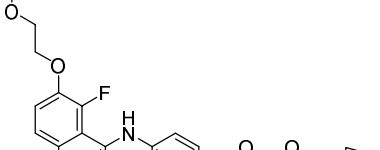
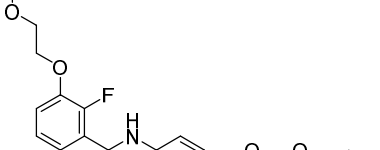
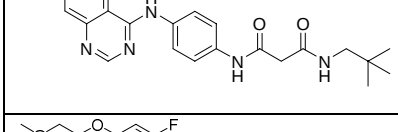
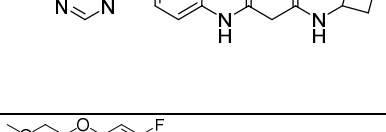
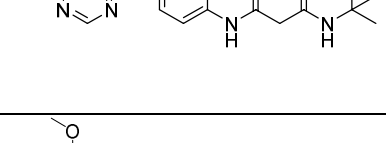
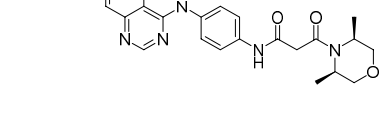
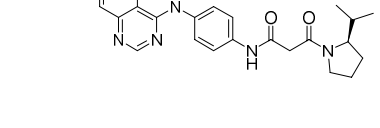
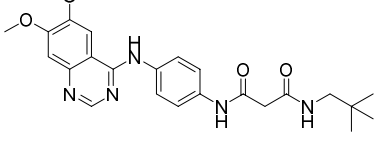
		
		
		
		
		
		
		
		
		
		
		
		
		
		

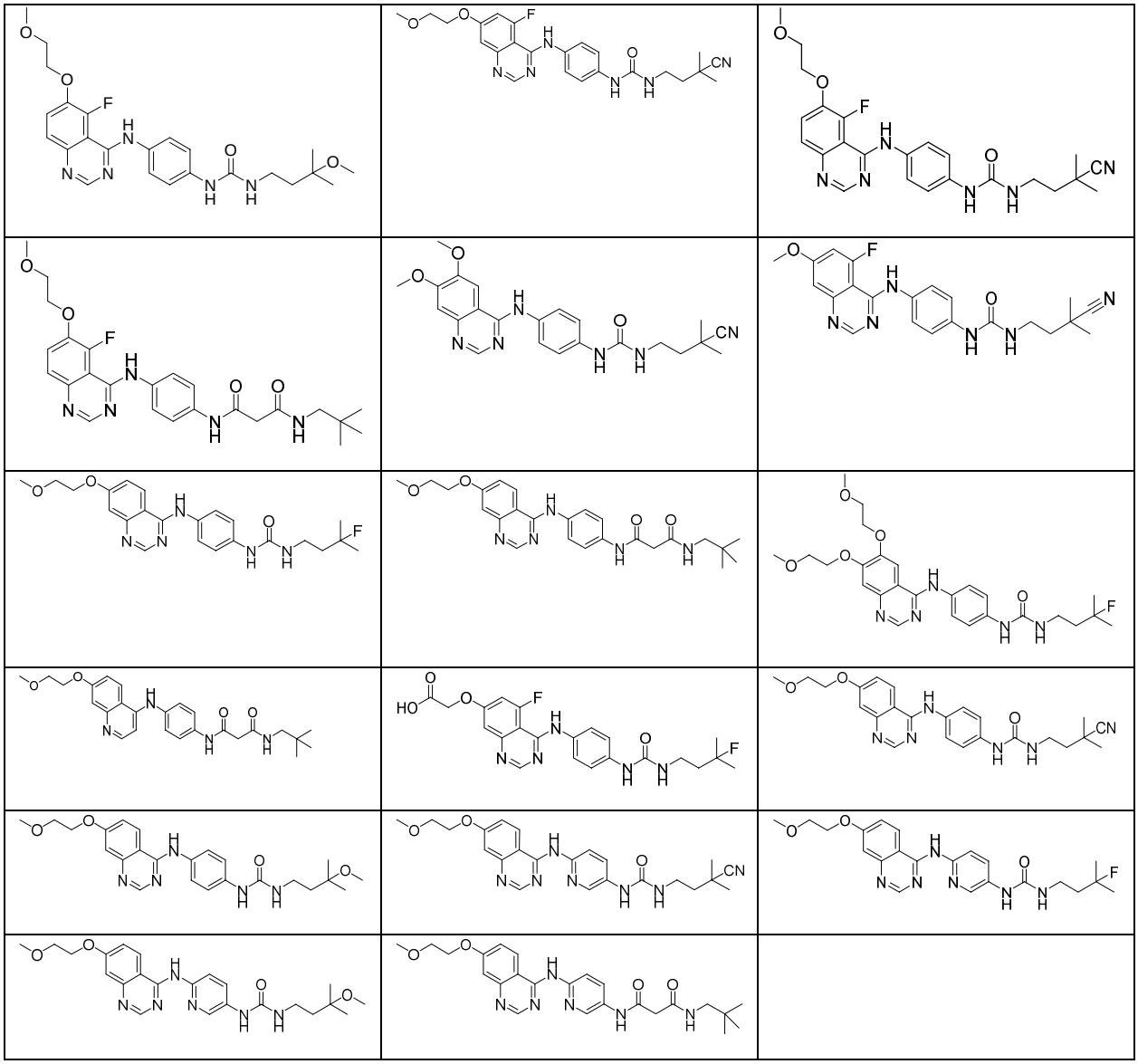
		
		
		
		
		
		
		
		
		
		
		
		
		



or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof.

17. A pharmaceutical composition comprising the compound according to any one of claims 1-16, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier or excipient.

18. The compound according to any one of claims 1-16, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, or the pharmaceutical composition of claim 17, for use in treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT activated gastrointestinal stromal tumors, PDGFRa activated gastrointestinal stromal tumors (GIST), melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma,

squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer in a patient in need thereof.

19. The compound or the pharmaceutical composition for the use according to claim 18, wherein

(i) the disease is gastrointestinal stromal tumors (GIST);

(ii) the disease is a KIT activated gastrointestinal stromal tumors (GIST),

optionally wherein the KIT activated gastrointestinal stromal tumors (GIST) has a baseline mutation selected from the group consisting of a KIT exon 9 mutation, a KIT exon 11 mutation, a KIT exon 13 mutation, a KIT exon 17 mutation, and a KIT exon 18 mutation;

(iii) the disease is a PDGFRa activated gastrointestinal stromal tumors (GIST),

optionally wherein the PDGFRa activated gastrointestinal stromal tumors (GIST) has a baseline mutation selected from PDGFRA D842V;

(iv) the disease is melanoma,

optionally wherein the melanoma is a KIT activated melanoma,

optionally wherein the KIT activated melanoma has a baseline mutation selected from the group consisting of a KIT exon 9 mutation, a KIT exon 11 mutation, a KIT exon 13 mutation, a KIT exon 17 mutation, and a KIT exon 18 mutation,

optionally wherein the melanoma is selected from the group consisting of cutaneous melanoma and noncutaneous melanoma,

optionally wherein the cutaneous melanoma is selected from the group consisting of superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, amelanotic melanoma, and desmoplastic melanoma,

optionally wherein the noncutaneous melanoma is selected from ocular melanoma and mucosal melanoma.

20. Use of the compound according to any one of claims 1-16, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, or the pharmaceutical composition of claim 17 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT activated gastrointestinal stromal tumors, PDGFRa activated gastrointestinal stromal tumors (GIST), melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

21. The use of claim 18, wherein

(i) the disease is gastrointestinal stromal tumors (GIST);

(ii) the disease is a KIT activated gastrointestinal stromal tumors (GIST),

optionally wherein the KIT activated gastrointestinal stromal tumors (GIST) has a baseline mutation selected from the group consisting of a KIT exon 9 mutation, a KIT exon 11 mutation, a KIT exon 13 mutation, a KIT exon 17 mutation, and a KIT exon 18 mutation;

(iii) the disease is a PDGFRa activated gastrointestinal stromal tumors (GIST),

optionally wherein the PDGFRa activated gastrointestinal stromal tumors (GIST) has a baseline mutation selected from PDGFRA D842V;

(iv) the disease is melanoma,

optionally wherein the melanoma is a KIT activated melanoma,

optionally wherein the KIT activated melanoma has a baseline mutation selected from the group consisting of a KIT exon 9 mutation, a KIT exon 11 mutation, a KIT exon 13 mutation, a KIT exon 17 mutation, and a KIT exon 18 mutation,

optionally wherein the melanoma is selected from the group consisting of cutaneous melanoma and noncutaneous melanoma,

optionally wherein the cutaneous melanoma is selected from the group consisting of superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, amelanotic melanoma, and desmoplastic melanoma, and

optionally wherein the noncutaneous melanoma is selected from ocular melanoma and mucosal melanoma.