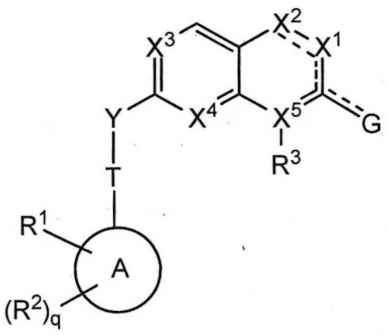
factor α (TNF-α)), and growth factors (e.g., granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

[0006] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY

[0007] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of one or more protein kinases. Such compounds have general formula **I**:



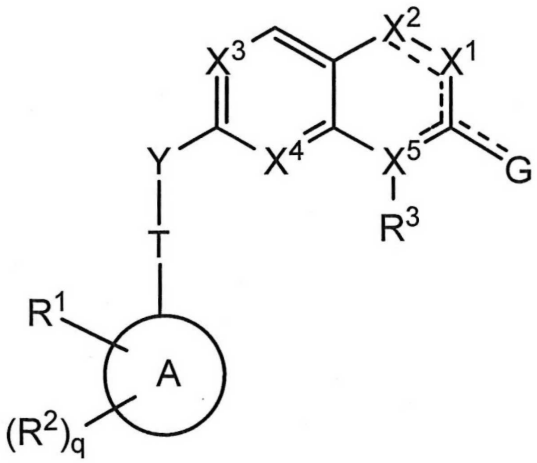
I

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, X^2, X^3, X^4, X^5, G, Y, T, and q, is as defined and described in embodiments herein. In certain embodiments, R^1 is a warhead group.

[0008] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with abnormal cellular responses triggered by protein kinase-mediated events. Such diseases, disorders, or conditions include those described herein.

[0009] Compounds provided by the present disclosure are also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

[0009a] In a first aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is $-NR^4$, N, $-CR^4R^{4'}$, or $-CR^4$;

X^2 is $-NR^5$, N, $-CR^5R^{5'}$, or $-CR^5$;

X^3 is N or CR^6

X^4 is N or CR^7;

X^5 is N, C, or CH; wherein at least one of X^1, X^2, X^3, X^4, or X^5 is N;

G is H, O, OR, or N(R)(R);

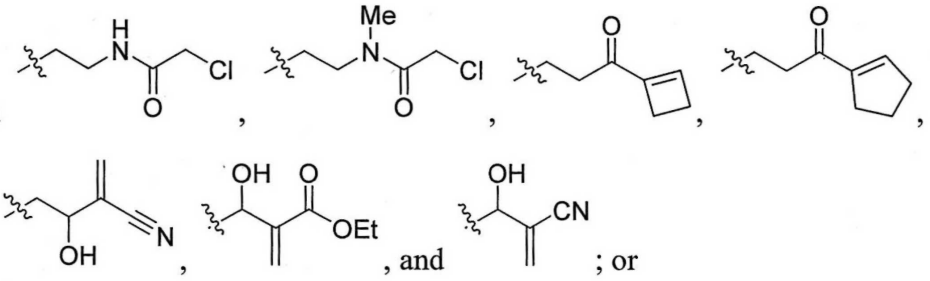
Ring A is an optionally substituted group selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-10 membered bicyclic saturated, partially unsaturated or aryl ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered

heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7 membered heterocyclic ring having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 4-7 membered heteroaryl ring having 0-4 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is a warhead group –L-Y; wherein R^1 is attached to an atom adjacent to the atom where T is attached, wherein:

R^1 is selected from  , and ; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one alkylidenyl double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one additional methylene unit of L is replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one triple bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or -C(O)O-; and

the Y group of R^1 is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with 1-4 R^e groups; or

L is a covalent bond, $–CH_2-$, -NH-, -C(O)-, $-CH_2NH-$, $-NHCH_2-$, –NHC(O)-, $-NHC(O)CH_2OC(O)-$, $-CH_2NHC(O)-$, $-NHSO_2-$, $-NHSO_2CH_2-$, or $-SO_2NH-$, and the Y group of R^1 is selected from:

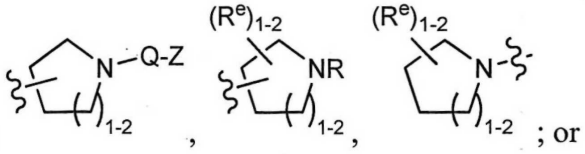
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups; or

(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups; or

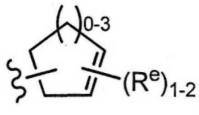
(*vi*) 

; or

(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

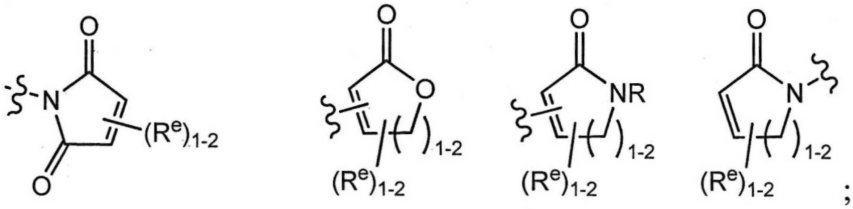
(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

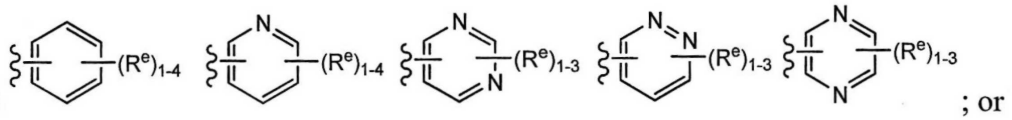
(*x*) 

; or

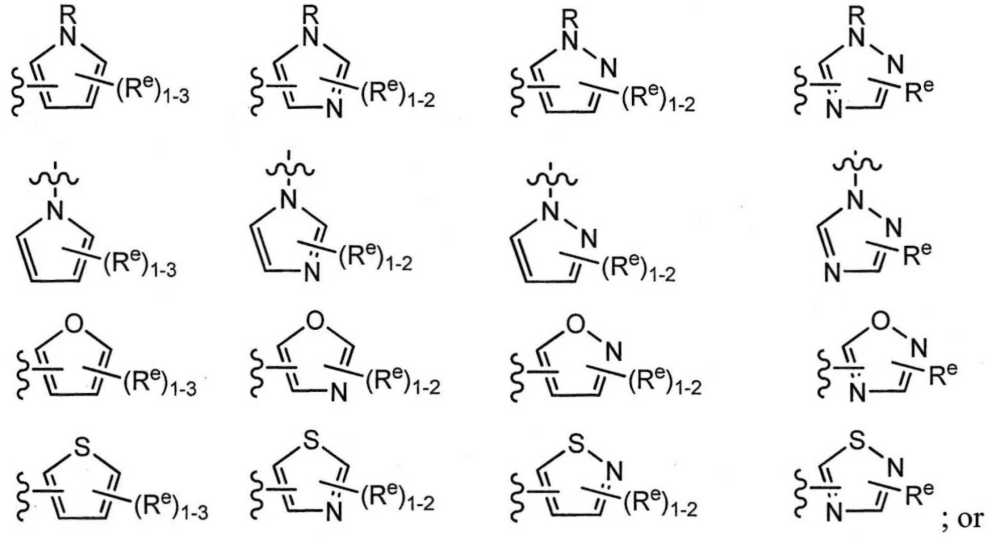
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*)  ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is a covalent bond, -C(O)-, -N(R)C(O)-, or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and the Y group of R^1 is selected from:

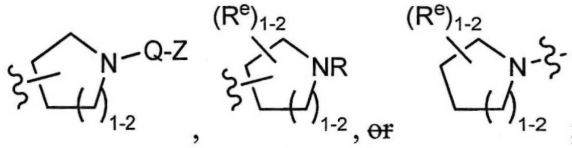
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups; or

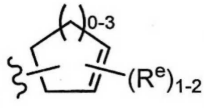
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*)  ; or

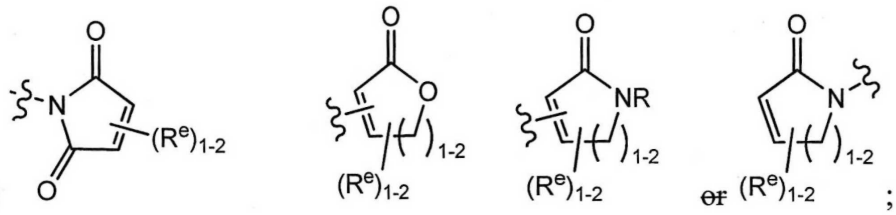
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

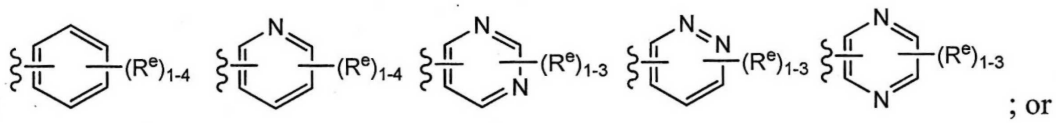
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*)  ; or

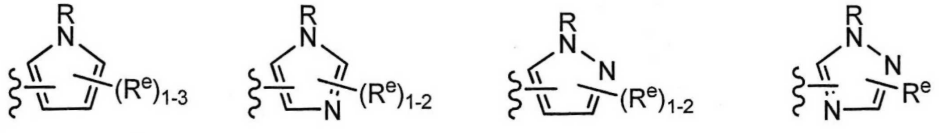
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

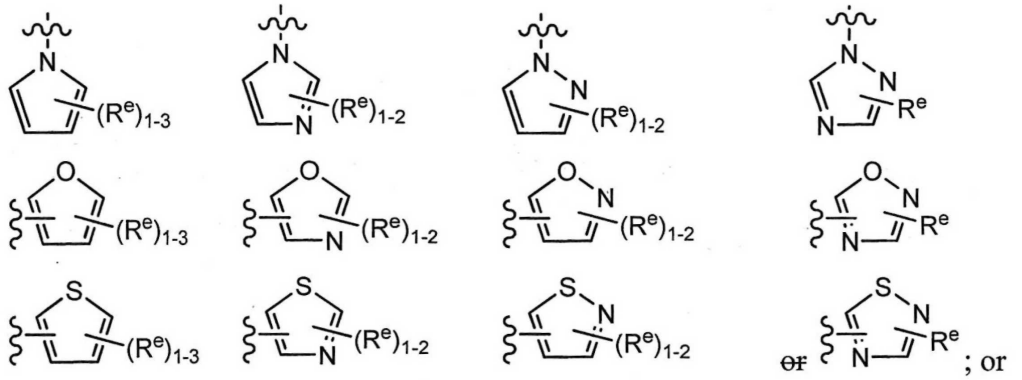
(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*) 



(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups;

each R^e is independently selected from –Q-Z, oxo, NO_2, halogen, CN, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a suitable leaving group selected from alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, or diazonium, wherein:

Q is a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-; and

each Z is independently hydrogen or C_{1-6} aliphatic substituted with oxo, halogen, NO_2, or CN;

each R^2 is independently –R, halogen, -haloalkyl, –OR, –SR, –CN, –NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N($R)_2$, -NRC(O)R, -NRC(O)N($R)_2$, -NRSO_2R, or –N($R)_2$;

R^3 is hydrogen, C_{2-6} alkenyl, -W-Cy, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-3 groups independently selected from halogen, –CN, oxo, –OR', or -C(O)O(C_{1-6} alkyl);

W is absent or is a bivalent C_{1-3} alkylene chain optionally substituted with one or more $R^{''}$ and wherein one methylene unit of W is optionally replaced with –O- , -S-, or -NR'-;

each $R^{'}$ is independently hydrogen or C_{1-6} alkyl;

each $R^{''}$ is independently halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-3 groups independently selected from halogen, –CN, oxo, or –OR';

Cy is phenyl, C_{3-7} cycloalkyl, or a 3-7 membered monocyclic or 5-10 membered bicyclic saturated, partially unsaturated, or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Cy is optionally substituted with 1-3 R^x;

each R^x is independently H, -CN, oxo, $-NH_2$, C_{1-6} alkyl, halogen, $-OR'$, $-N(R')_2$, $-NHC(O)(C_{1-6}$ alkyl), $-C(O)N(R')_2$, $-C(O)O(C_{1-6}$ alkyl), $-NHSO_2(C_{1-6}$ alkyl), or $-SO_2N(R')_2$;

or R^3 is absent if not allowed by valence;

each of R^4 and $R^{4'}$ is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring which is optionally bridged, a 4-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-10 membered bicyclic saturated, partially unsaturated or aryl ring, which is optionally bridged;

each of R^5 and $R^{5'}$ is independently –R, halogen, –OR, –SR, –CN, $–NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$;

Y is O or NR^a;

R^a is hydrogen or an optionally substituted C_{1-6} aliphatic group;

T is a covalent bond or a bivalent straight or branched, saturated or unsaturated C_{1-6} hydrocarbon chain wherein one or more methylene units are optionally replaced by -O-, -S-, -N(R)-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)N(R)-, -S(O)-, $-SO_2-$, $-SO_2N(R)-$, $-N(R)SO_2-$, or $-N(R)SO_2N(R)-$;

q is 0-6; and

each of R^6 and R^7 is independently –R, halogen, –OR, –SR, –CN, $–NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$.

[0009b] In a second aspect of the present disclosure, there is provided a composition comprising a compound as described herein, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

[0009c] In a third aspect of the present disclosure, there is provided a composition comprising the compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1:** Mass Modification of FGFR4 by **I-1**.

[0011] **Figure 2:** Data showing that compound **I-69** has prolonged duration of action (PDA) against pFGFR4 signalling in MDA-MB-453 cells consistent with the resynthesis rate of FGFR4.

[0012] **Figure 3:** Data showing that compound **I-1** has PDA against pFGFR4 signalling in MDA-MB-453 cells consistent with the resynthesis rate of FGFR4, whereas its noncovalent, reversible analog, **I-234** does not have PDA.

[0013] **Figure 4:** The amino acid sequence of FGFR4 (SEQ ID NO. 1).

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention

[0014] In certain embodiments, the present invention provides irreversible inhibitors of FGFR4. In some embodiments, such compounds include those of the formulae described herein, or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

2. Compounds and Definitions

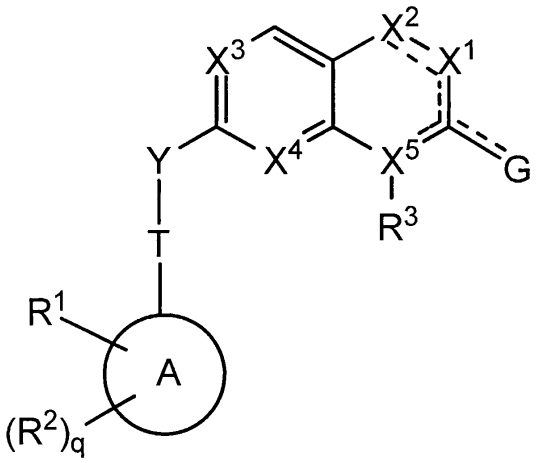
[0015] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0016] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely

CLAIMS

We claim:

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is $-NR^4$, N, $-CR^4R^{4'}$, or $-CR^4$;

X^2 is $-NR^5$, N, $-CR^5R^{5'}$, or $-CR^5$;

X^3 is N or CR^6

X^4 is N or CR^7;

X^5 is N, C, or CH; wherein at least one of X^1, X^2, X^3, X^4, or X^5 is N;

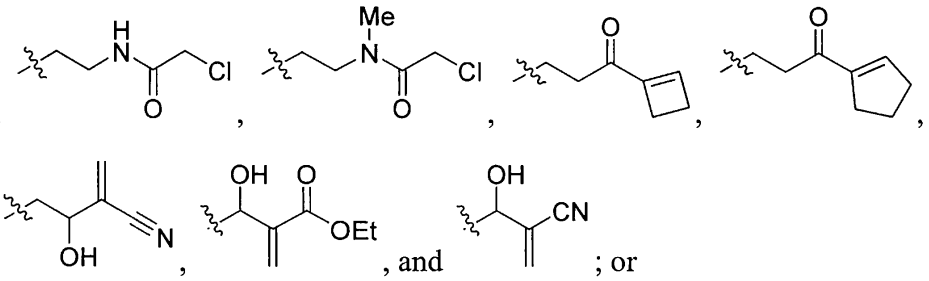
G is H, O, OR, or N(R)(R);

Ring A is an optionally substituted group selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-10 membered bicyclic saturated, partially unsaturated or aryl ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7 membered heterocyclic ring having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 4-7 membered heteroaryl ring having 0-4 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is a warhead group –L-Y; wherein R^1 is attached to an atom adjacent to the atom where T is attached, wherein:

R^1 is selected from  , and ; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one alkylidenyl double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one additional methylene unit of L is replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one triple bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or -C(O)O-; and

the Y group of R^1 is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or

aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with 1-4 R^e groups; or

L is a covalent bond, $-CH_2-$, -NH-, -C(O)-, $-CH_2NH-$, $-NHCH_2-$, –NHC(O)-, $-NHC(O)CH_2OC(O)-$, $-CH_2NHC(O)-$, $-NHSO_2-$, $-NHSO_2CH_2-$, or $-SO_2NH-$, and the Y group of R^1 is selected from:

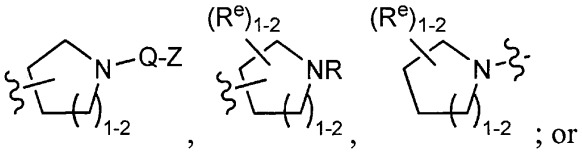
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups; or

(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups; or

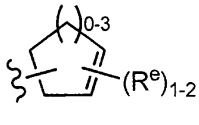
(*vi*) 

; or

(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

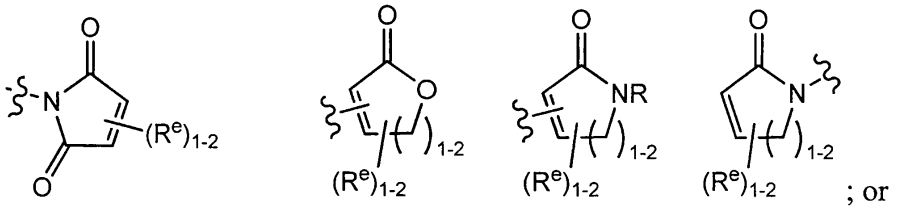
(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

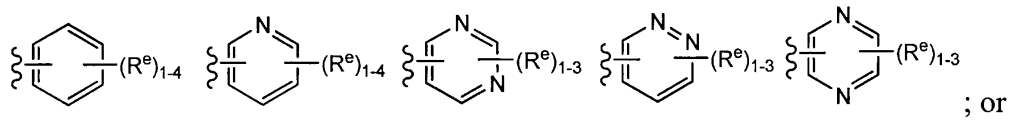
(*x*) 

; or

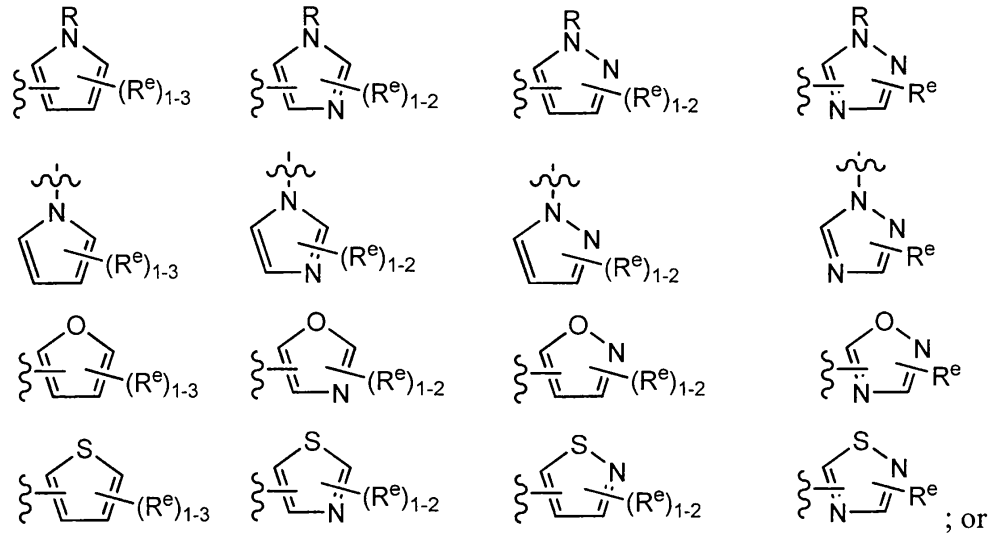
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*)  ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is a covalent bond, -C(O)-, -N(R)C(O)-, or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and the Y group of R^1 is selected from:

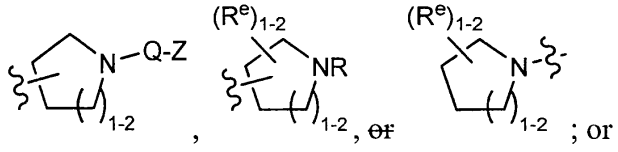
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups; or

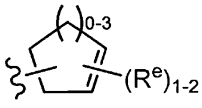
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*)  ; or

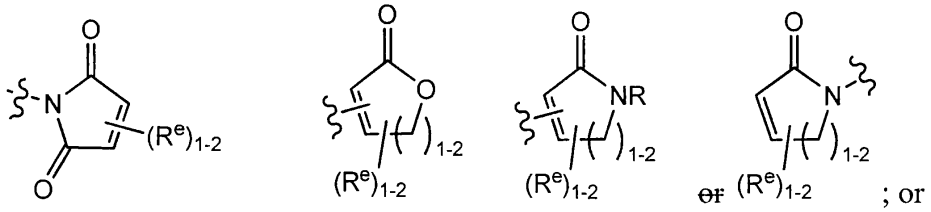
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

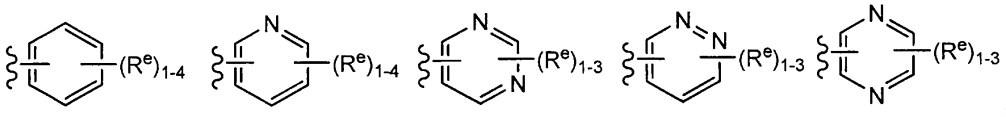
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*)  ; or

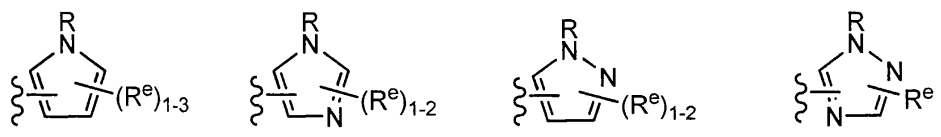
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

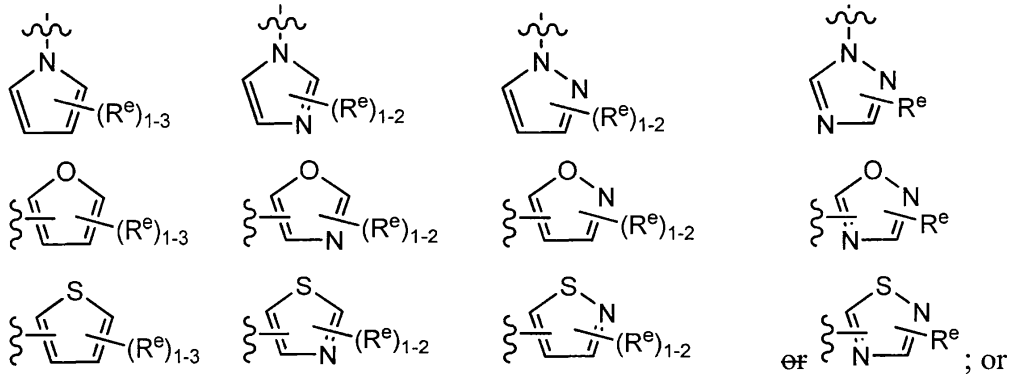
(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*) 



(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups;

each R^e is independently selected from –Q-Z, oxo, NO_2, halogen, CN, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a suitable leaving group selected from alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, or diazonium, wherein:

Q is a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-; and

each Z is independently hydrogen or C_{1-6} aliphatic substituted with oxo, halogen, NO_2, or CN;

each R^2 is independently –R, halogen, -haloalkyl, –OR, –SR, –CN, –NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N($R)_2$, -NRC(O)R, -NRC(O)N($R)_2$, -NRSO_2R, or –N($R)_2$;

R^3 is hydrogen, C_{2-6} alkenyl, -W-Cy, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-3 groups independently selected from halogen, –CN, oxo, –OR', or -C(O)O(C_{1-6} alkyl);

W is absent or is a bivalent C_{1-3} alkylene chain optionally substituted with one or more R'' and wherein one methylene unit of W is optionally replaced with –O- , -S-, or -NR'-;

each R' is independently hydrogen or C_{1-6} alkyl;

each $R^{''}$ is independently halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1-3 groups independently selected from halogen, –CN, oxo, or –OR';

Cy is phenyl, C_{3-7} cycloalkyl, or a 3-7 membered monocyclic or 5-10 membered bicyclic saturated, partially unsaturated, or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Cy is optionally substituted with 1-3 R^x;

each R^x is independently H, -CN, oxo, $-NH_2$, C_{1-6} alkyl, halogen, $-OR^{'}$, $-N(R')_2$, $-NHC(O)(C_{1-6}$ alkyl), $-C(O)N(R')_2$, $-C(O)O(C_{1-6}$ alkyl), $-NHSO_2(C_{1-6}$ alkyl), or $-SO_2N(R')_2$;

or R^3 is absent if not allowed by valence;

each of R^4 and $R^{4'}$ is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring which is optionally bridged, a 4-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-10 membered bicyclic saturated, partially unsaturated or aryl ring, which is optionally bridged;

each of R^5 and $R^{5'}$ is independently –R, halogen, –OR, –SR, –CN, $-NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$;

Y is O or NR^a;

R^a is hydrogen or an optionally substituted C_{1-6} aliphatic group;

T is a covalent bond or a bivalent straight or branched, saturated or unsaturated C_{1-6} hydrocarbon chain wherein one or more methylene units are optionally replaced by -O-, -S-, -N(R)-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)N(R)-, -S(O)-, $-SO_2-$, $-SO_2N(R)-$, $-N(R)SO_2-$, or $-N(R)SO_2N(R)-$;

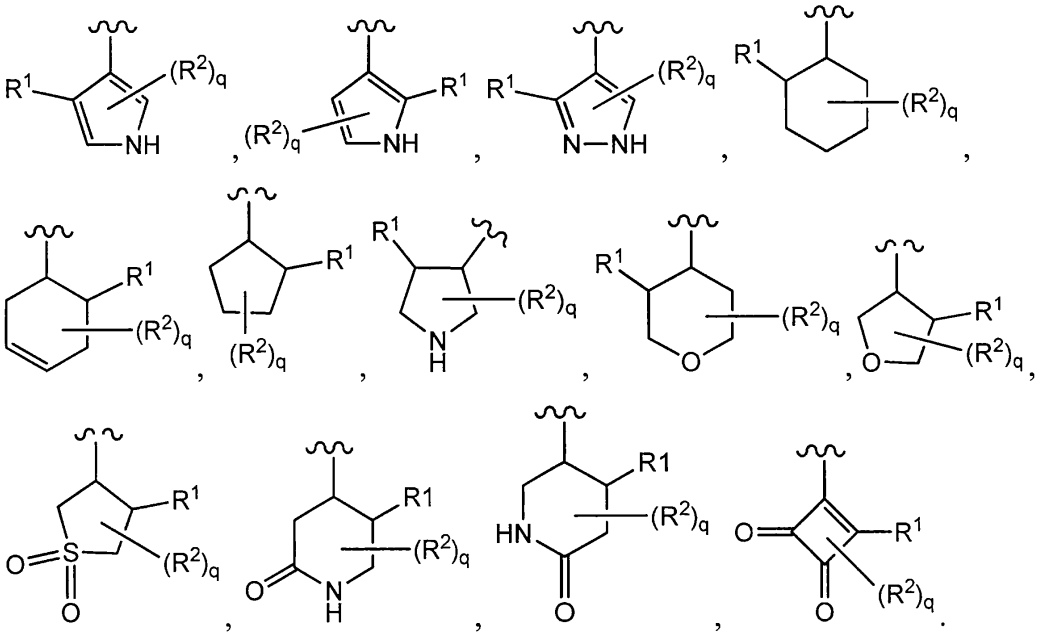
q is 0-6; and

each of R^6 and R^7 is independently –R, halogen, –OR, –SR, –CN, $-NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$.

2. The compound according to claim 1, wherein Ring A is cyclohexyl, cyclohexenyl, cyclopentyl, cyclobutyl, cyclopropyl, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole,

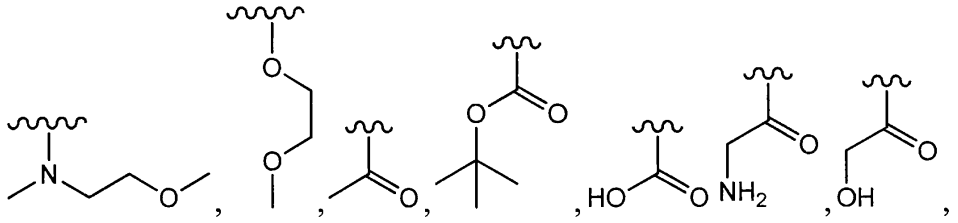
pyrazole, piperidine, piperidin-one, pyrrolidine, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene dioxide, or cyclobutene dione.

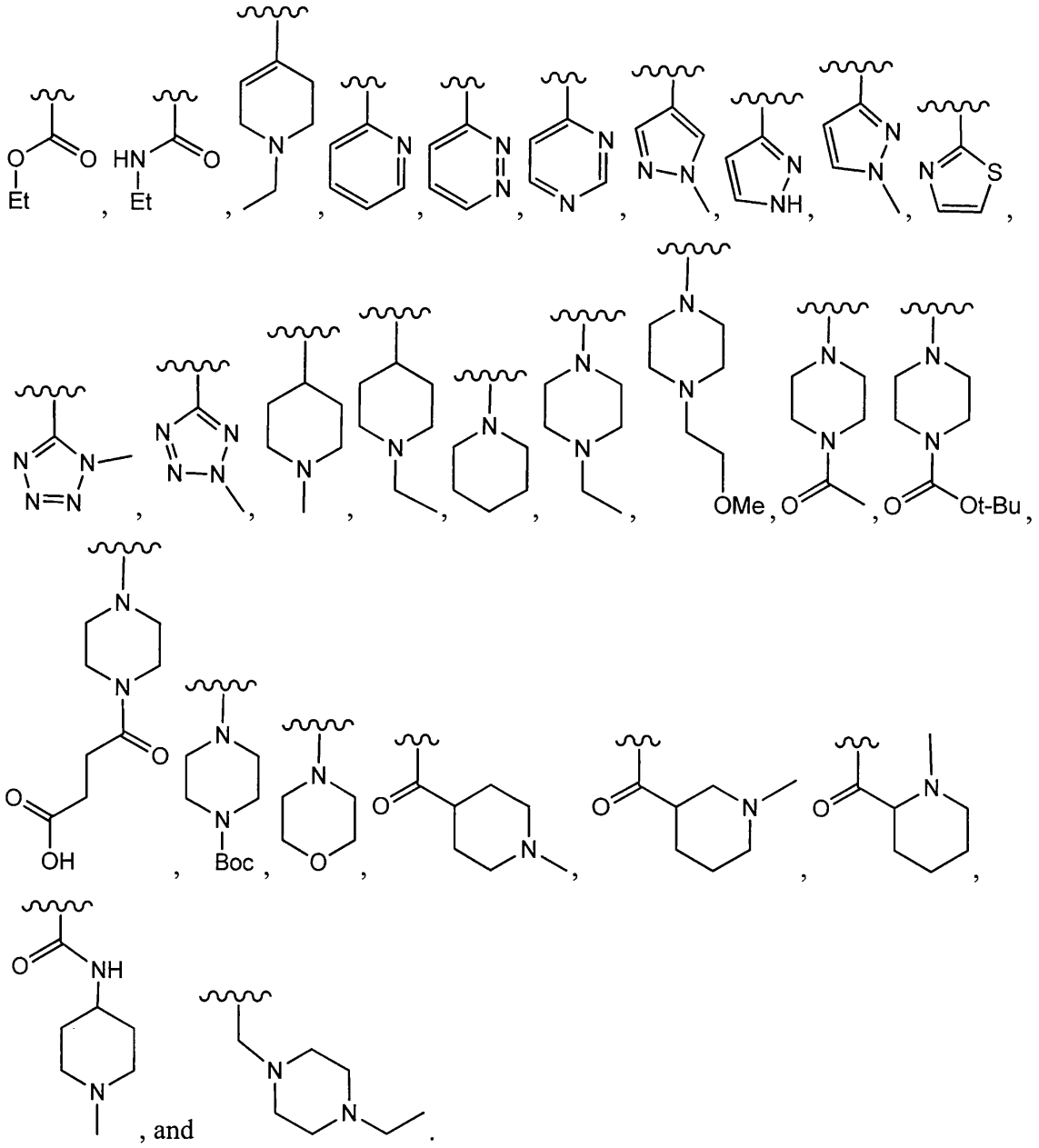
3. The compound according to claim 1, wherein Ring A is



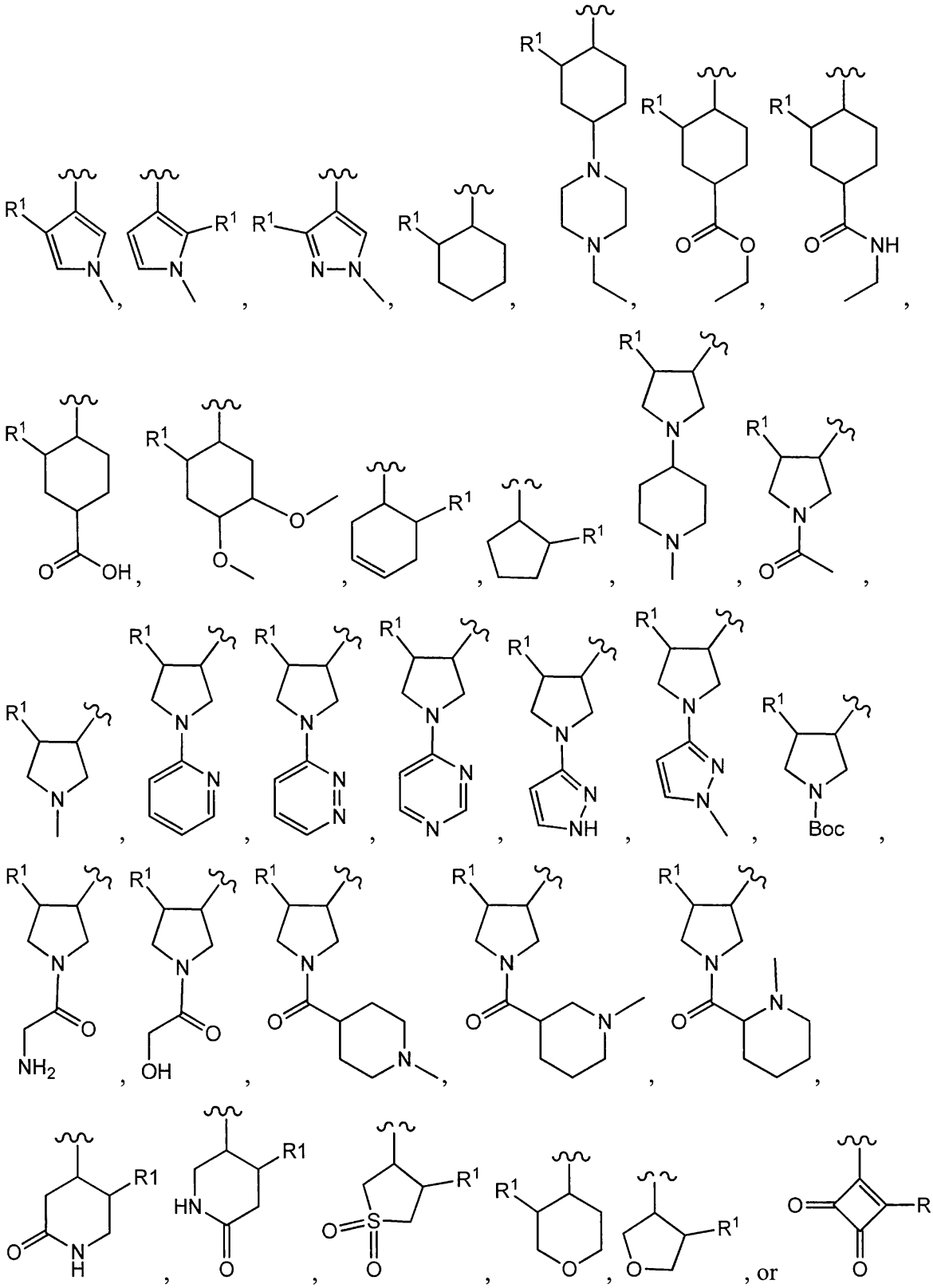
4. The compound according to claim 3, wherein each R^2 is independently halogen, -haloalkyl, –OR, –SR, –CN, –NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N$(R)_2$, -NRC(O)R, -NRC(O)N$(R)_2$, -$NRSO_2R$, or –N$(R)_2$.

5. The compound according to claim 3, wherein each R^2 is independently -CH_3, -Cl, -F, -CF_3, or -OMe; or is selected from

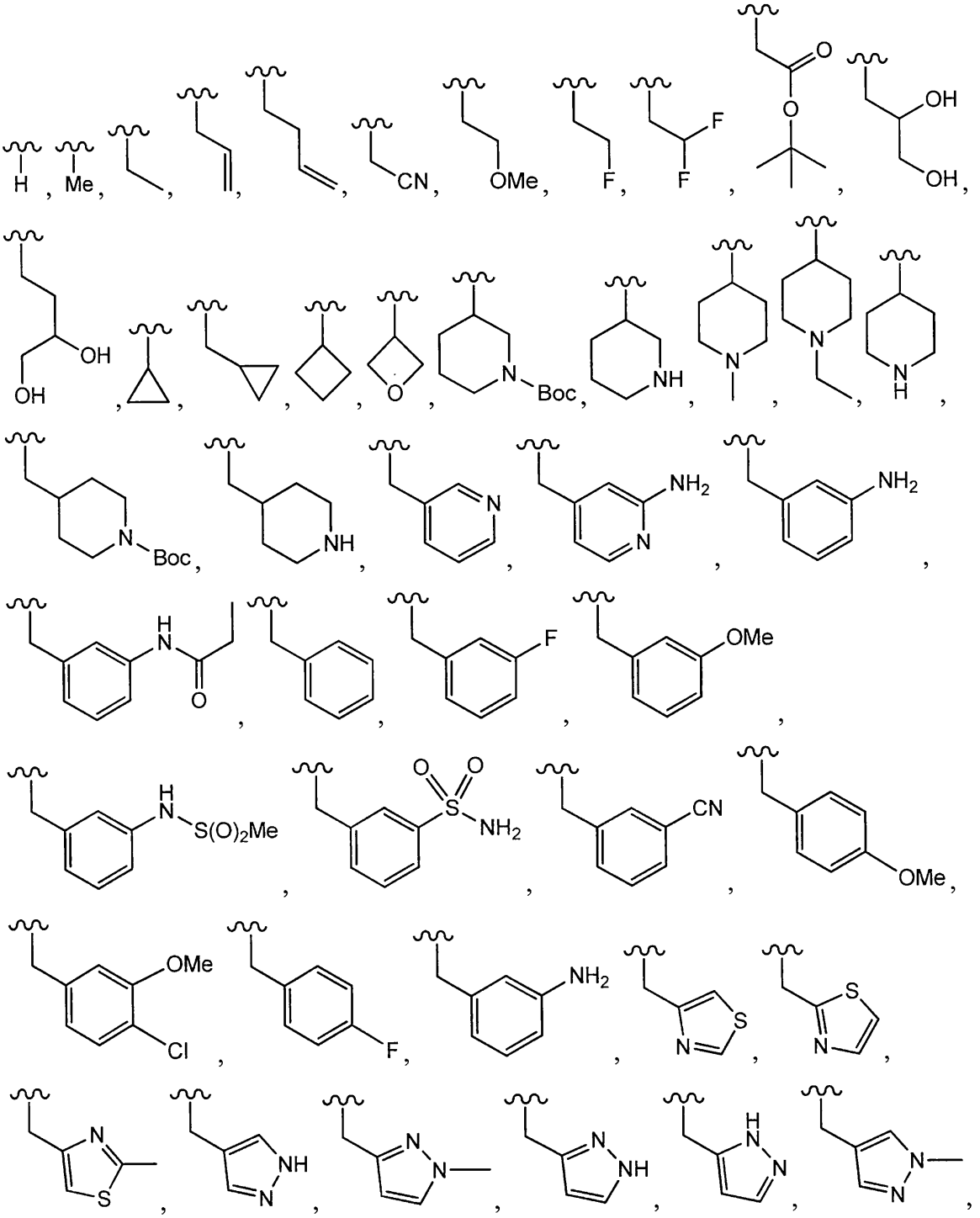


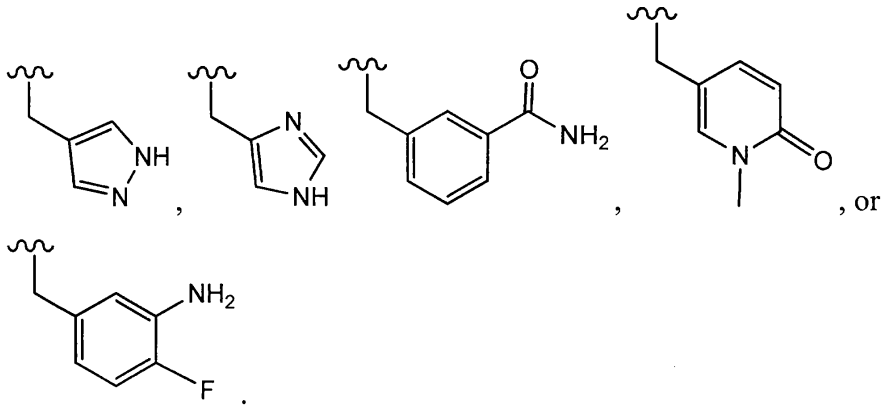


6. The compound according to claim 1, wherein Ring A is selected from:



7. The compound according to claim 1, wherein R^3 is

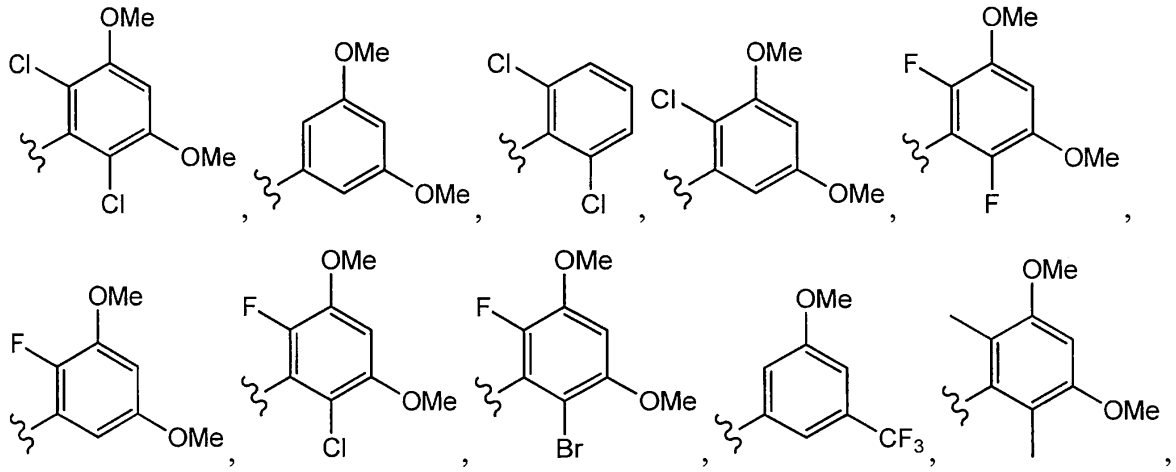


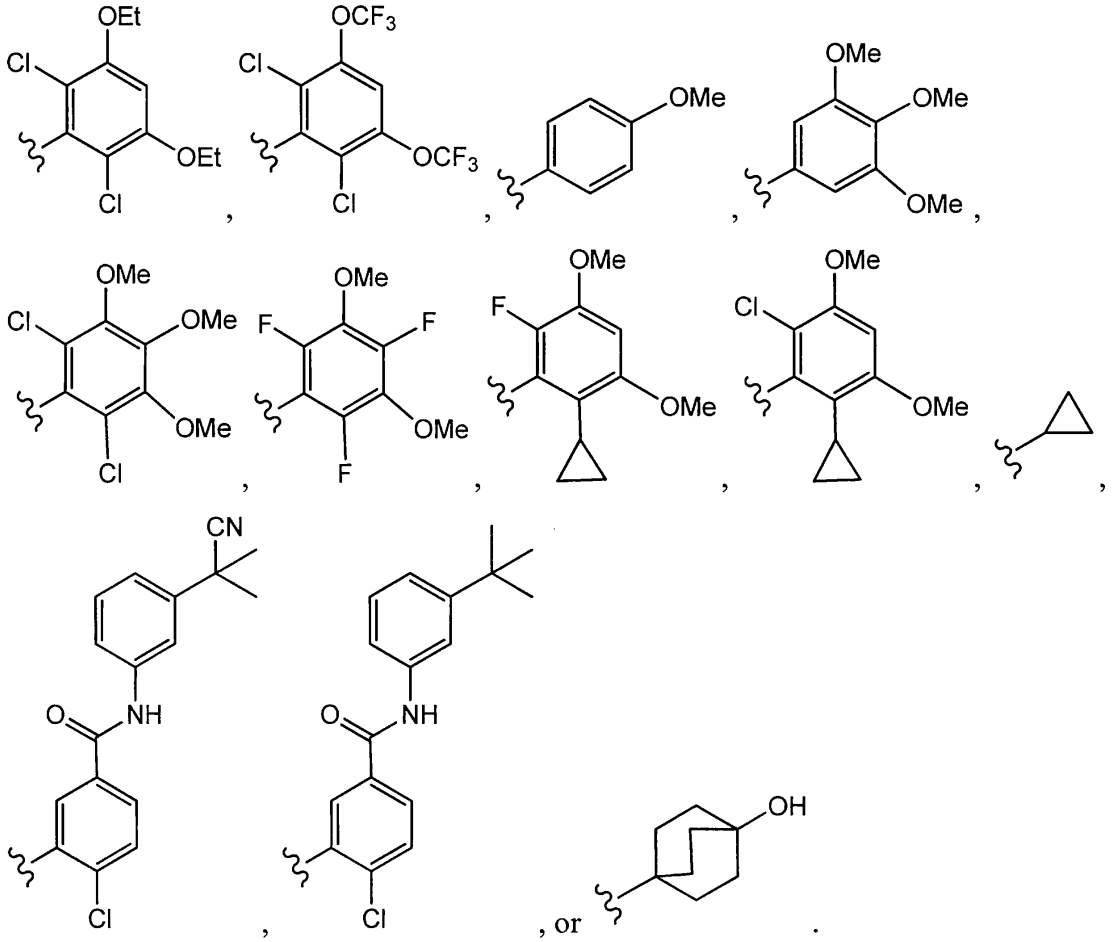


8. The compound according to claim 1, wherein R^4 is an optionally substituted phenyl.

9. The compound according to claim 1, wherein R^4 is an optionally substituted C_{1-6} aliphatic, or an optionally substituted ring selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

10. The compound according to claim 1, wherein R^4 is ethyl, phenyl, cyclohexyl,



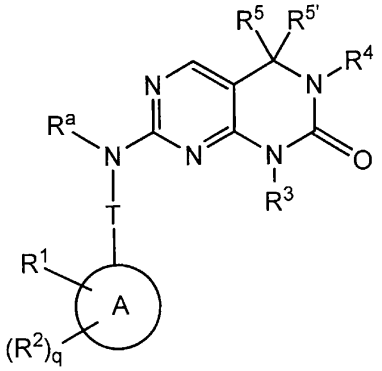


11. The compound according to claim 1, wherein each of R^5 and $R^{5'}$ is independently H, or –Me.

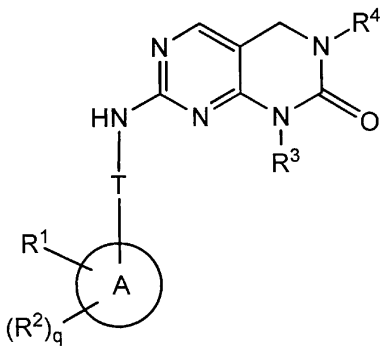
12. The compound according to claim 1, wherein T is a covalent bond.

13. The compound according to claim 1, wherein T is a bivalent straight or branched, saturated or unsaturated C_{1-6} hydrocarbon chain wherein one or more methylene units are optionally replaced by -O-, -S-, -N(R)-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)N(R)-, $-N(R)SO_2-$, or $-N(R)SO_2N(R)-$.

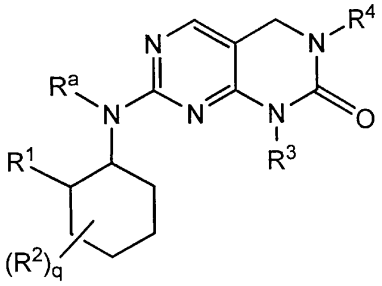
14. The compound of claim 1, wherein said compound is of one of the following formulae:



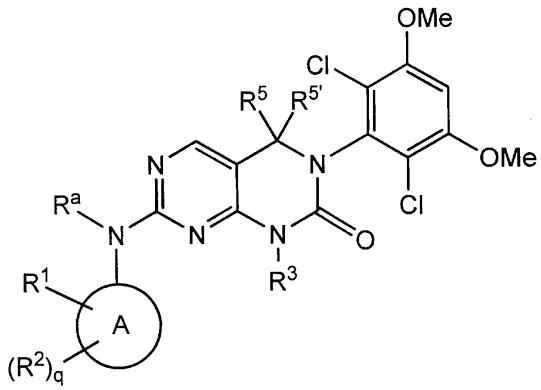
I-a



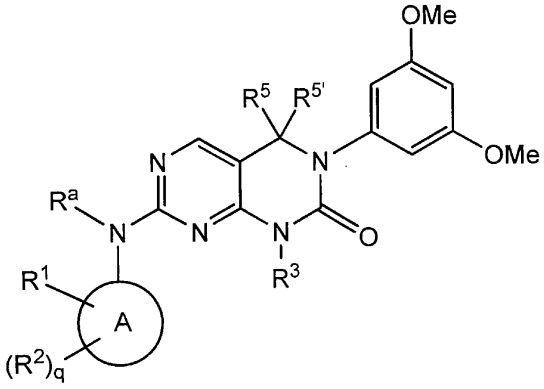
I-b



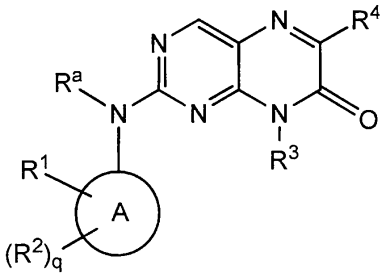
I-d



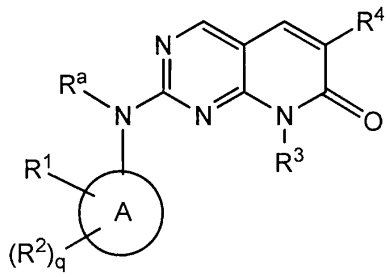
I-e



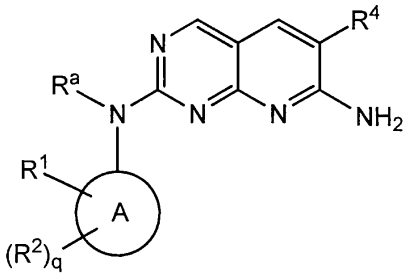
I-f



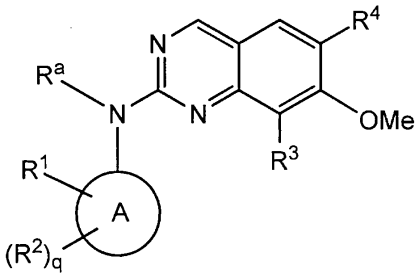
I-g



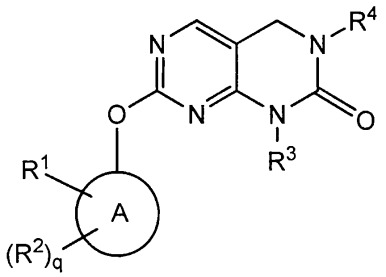
I-h



I-j

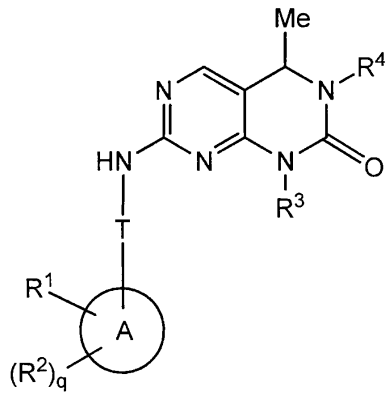


I-k



I-n

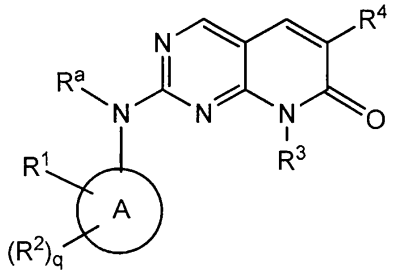
or



I-q

or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein the compound is a compound of formula **I-h**:

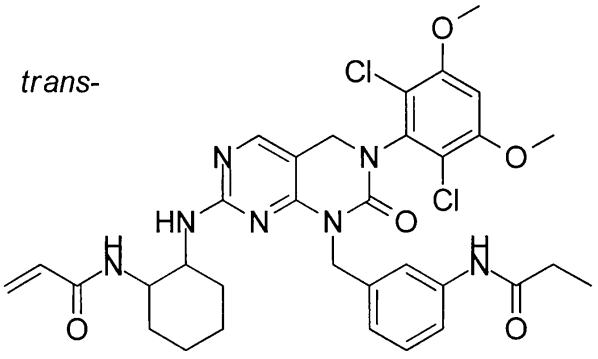


I-h

or a pharmaceutically acceptable salt thereof.

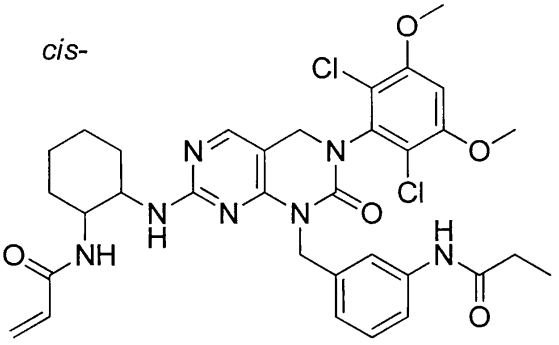
16. The compound according to claim 1, selected from

trans-

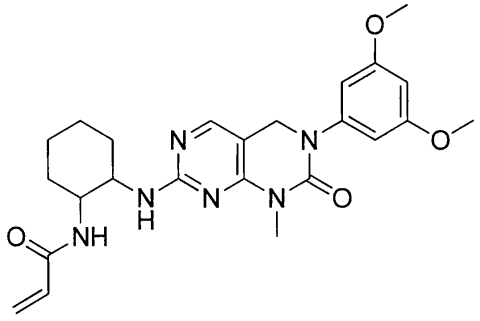


I-7

cis-

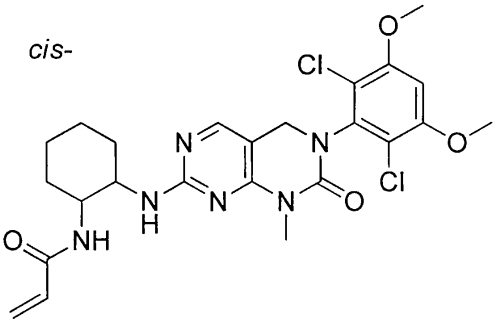


I-8

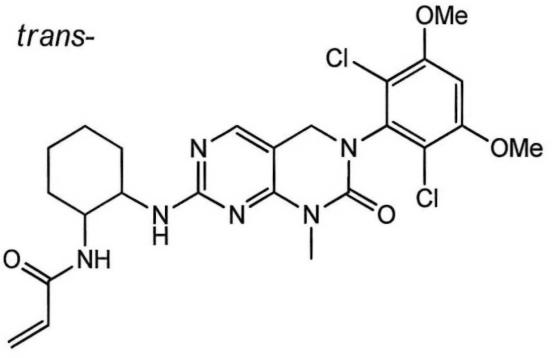


I-18

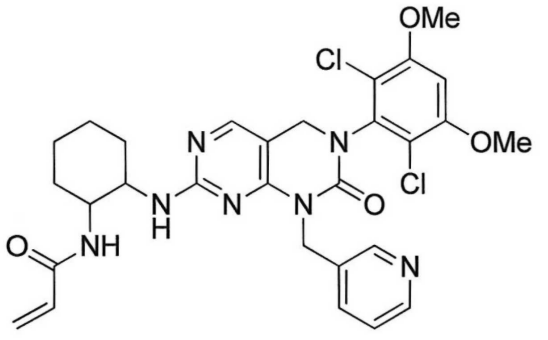
cis-



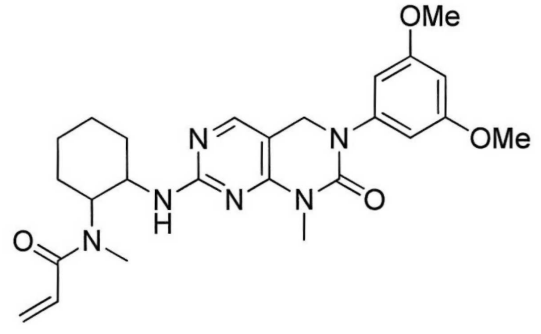
I-19



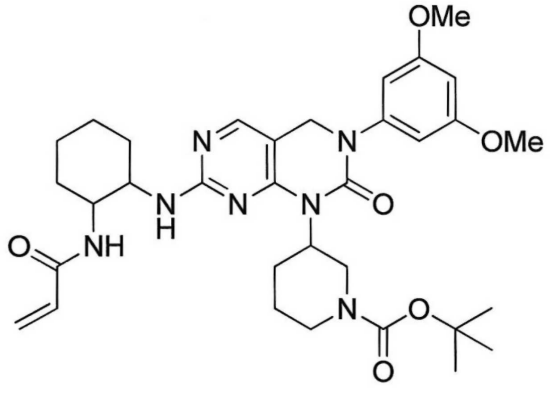
I-22



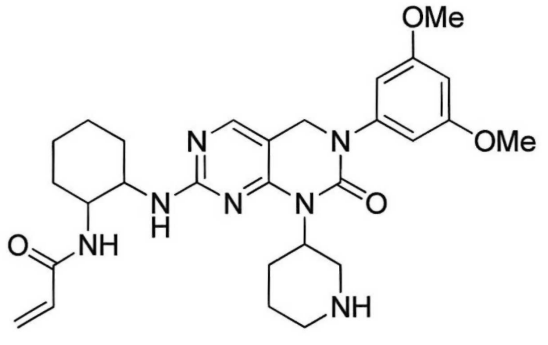
I-35



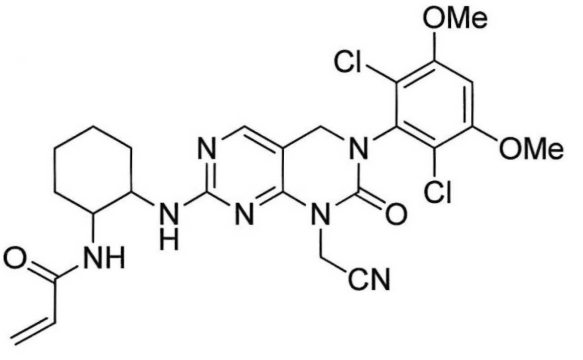
I-39



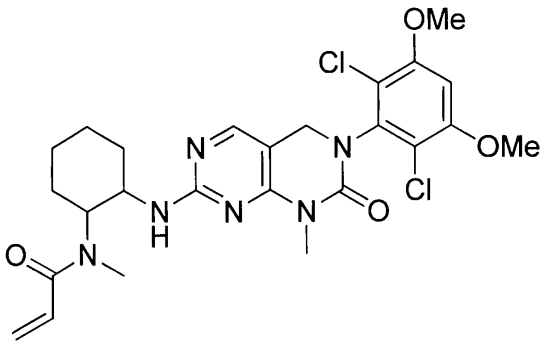
I-45



I-46



I-47



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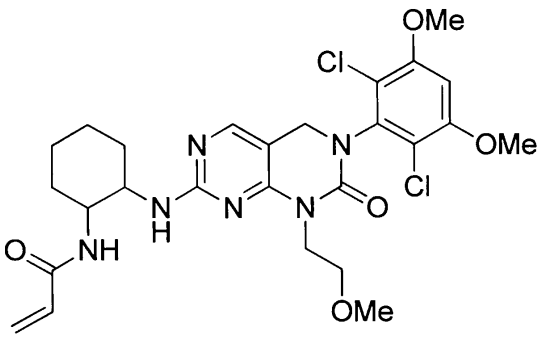

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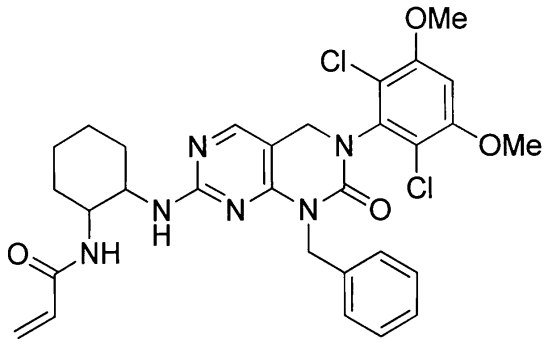

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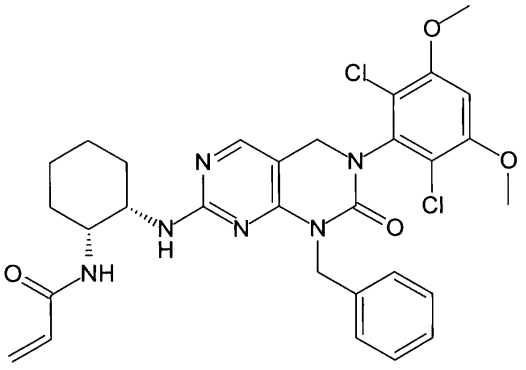

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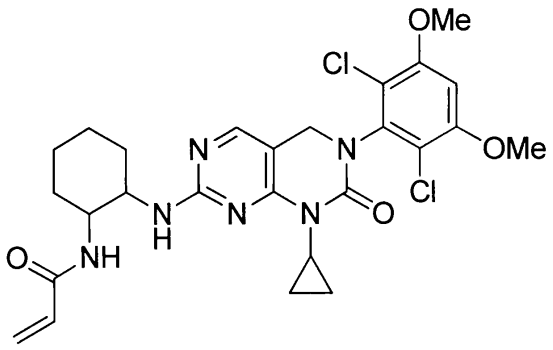

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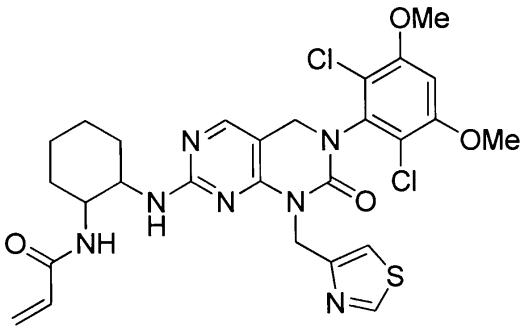

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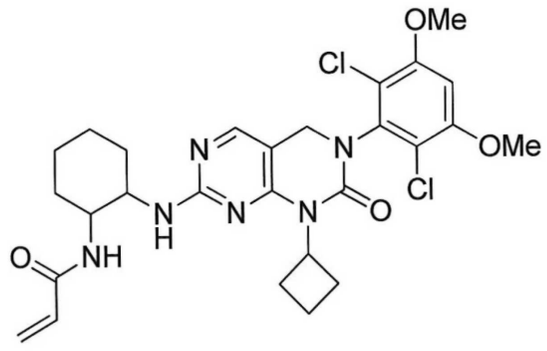

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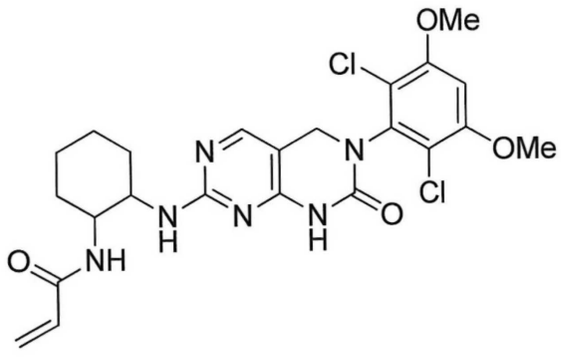

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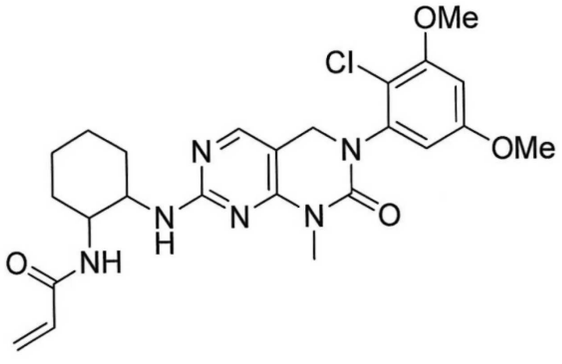

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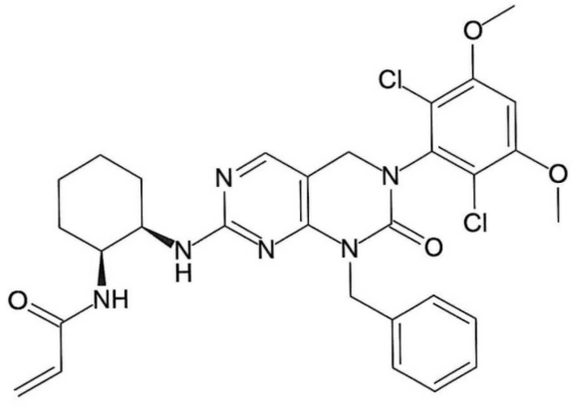

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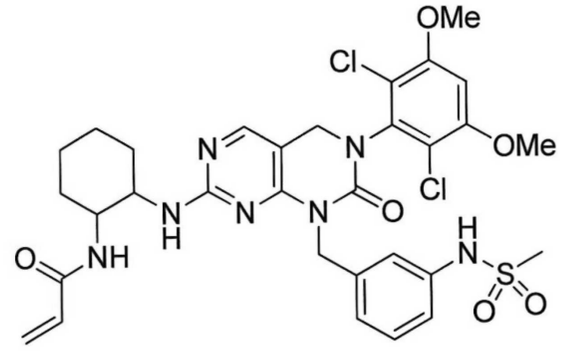

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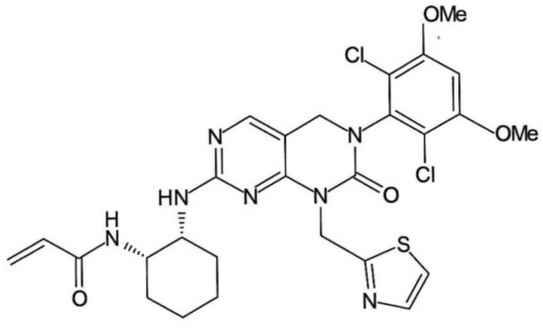

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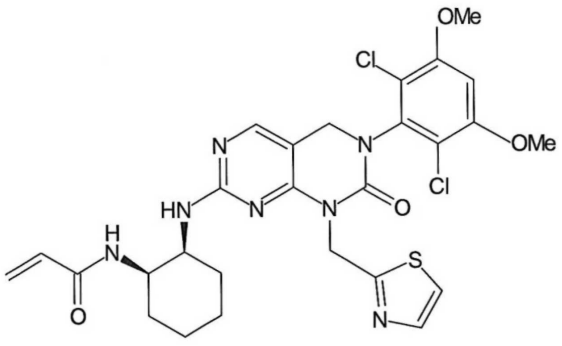

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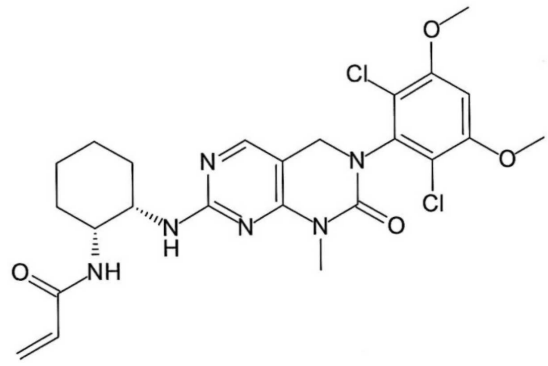

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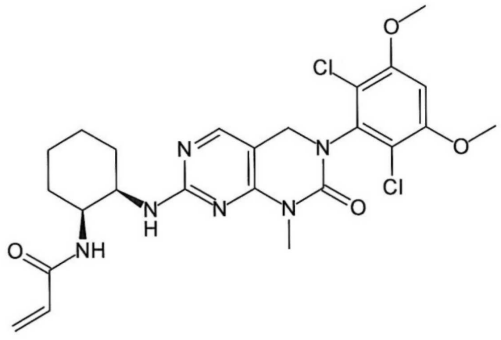

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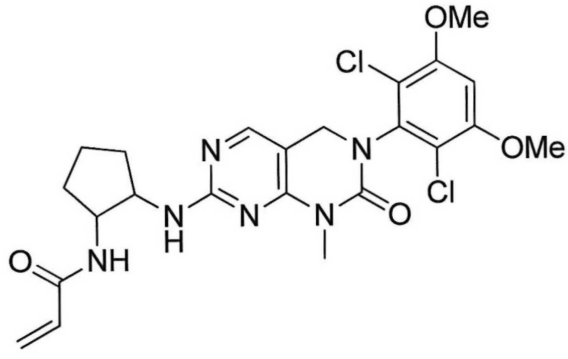

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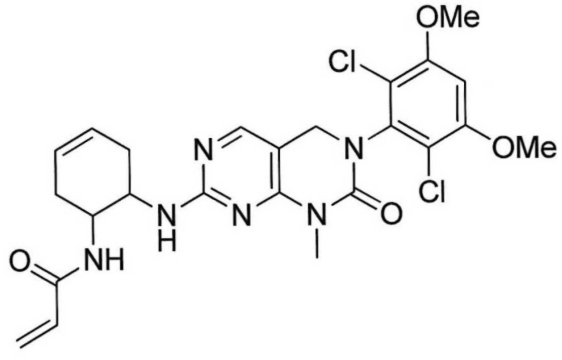

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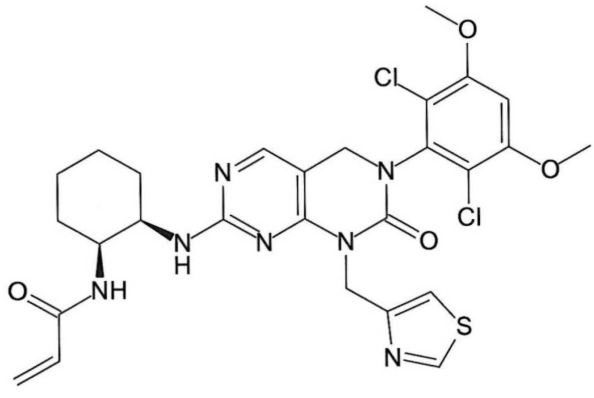

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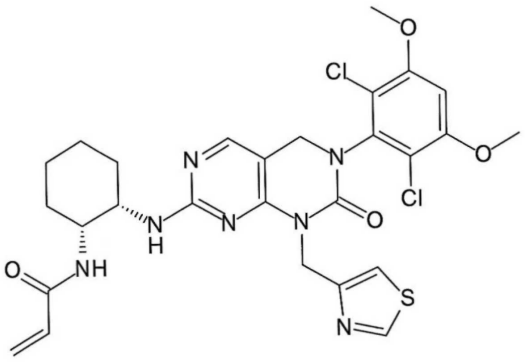

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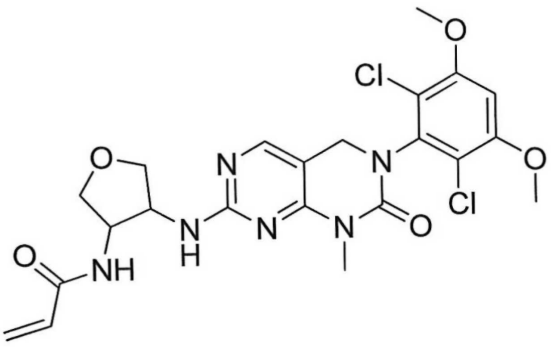

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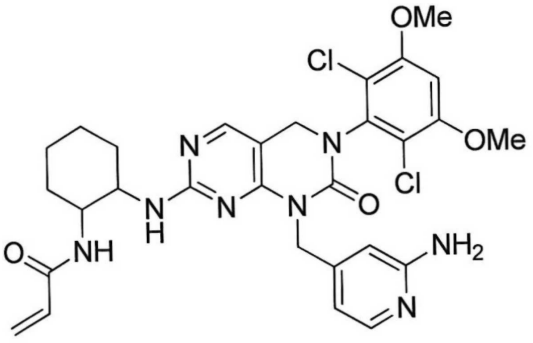

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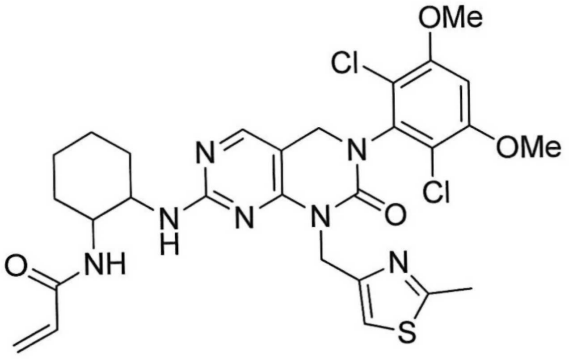

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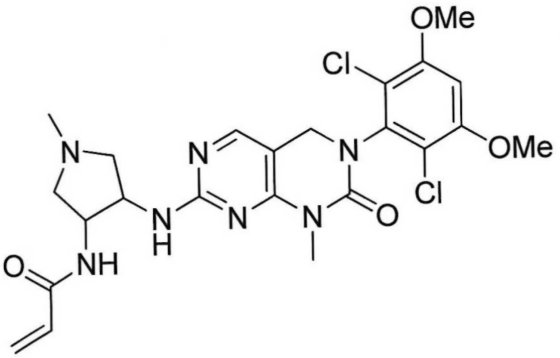

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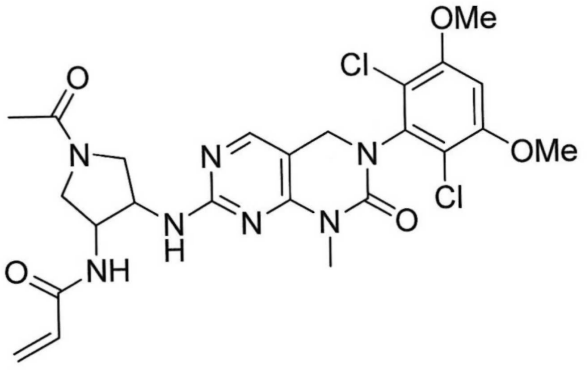

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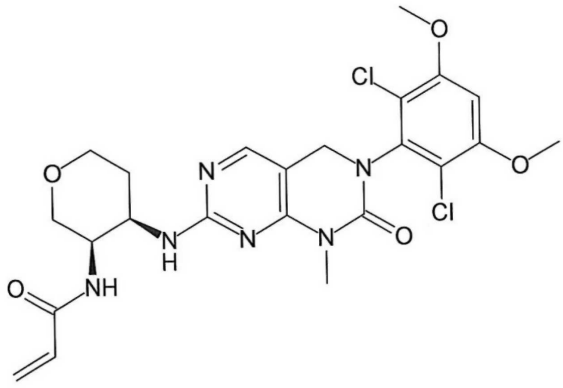

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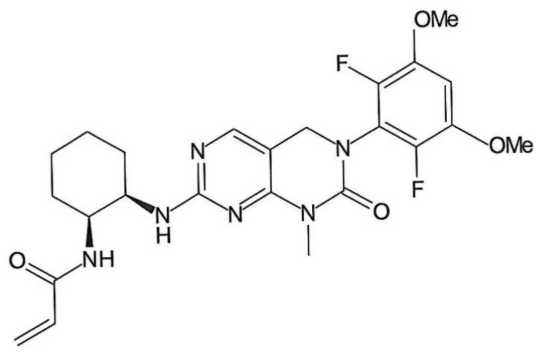

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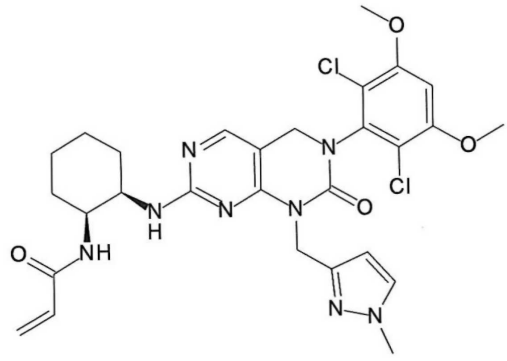

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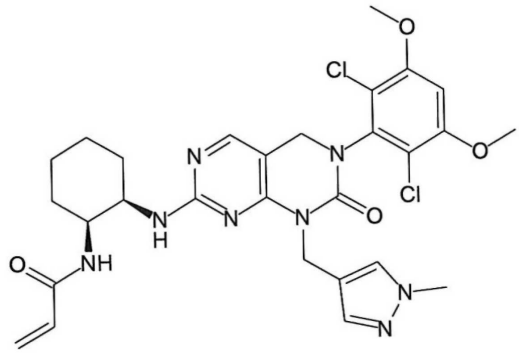

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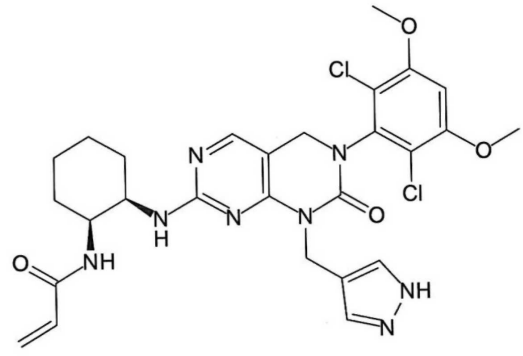

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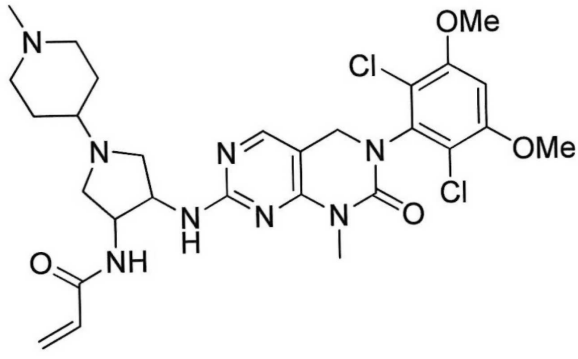

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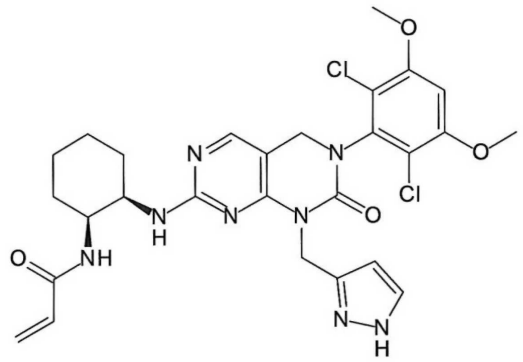

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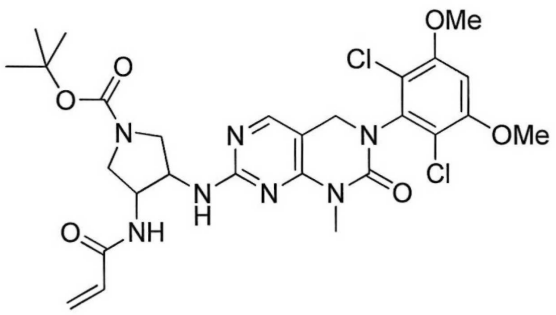

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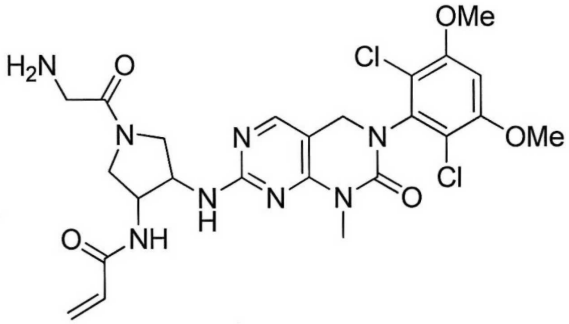

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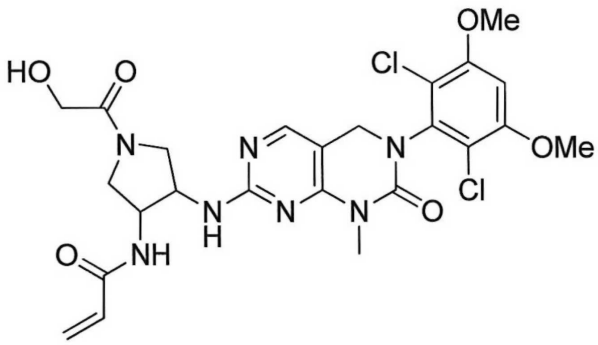

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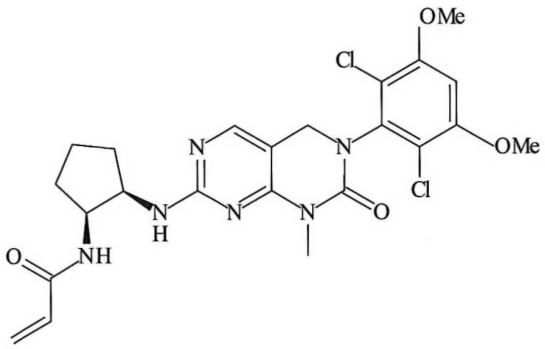

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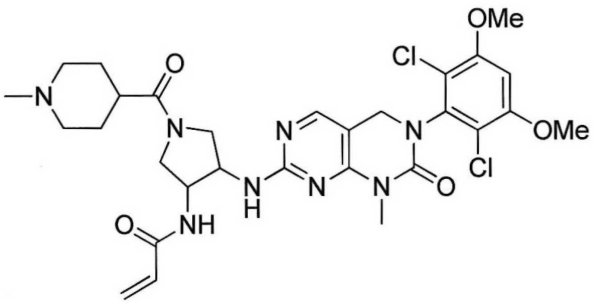

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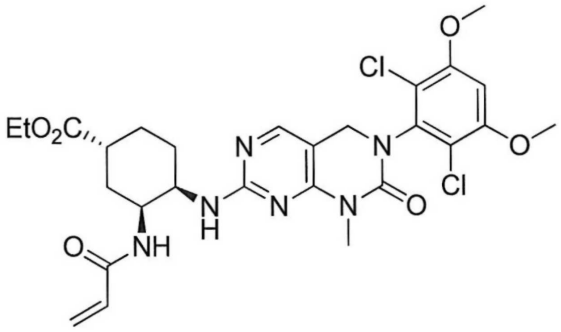

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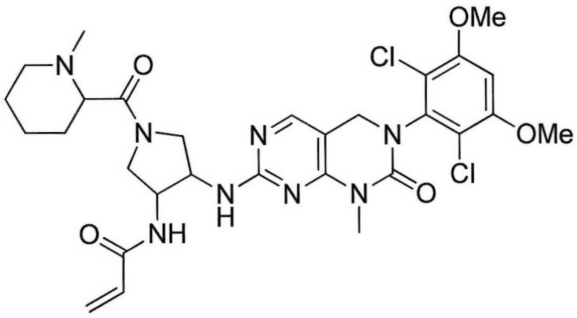

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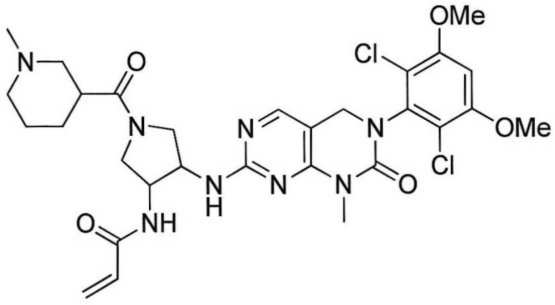

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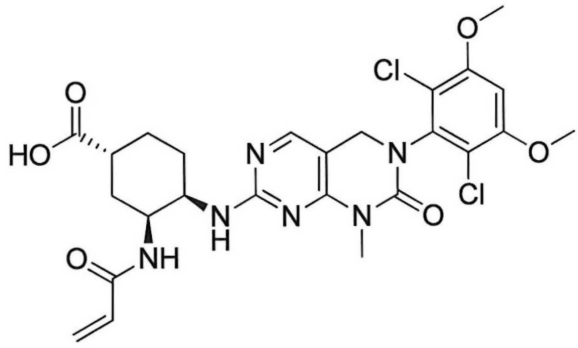

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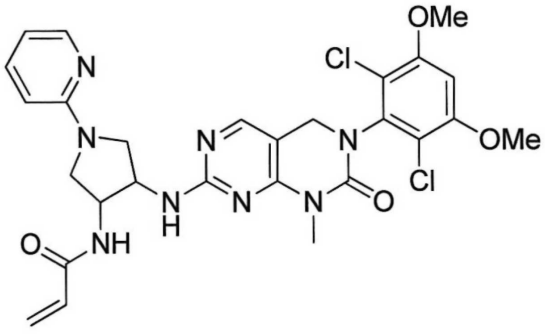

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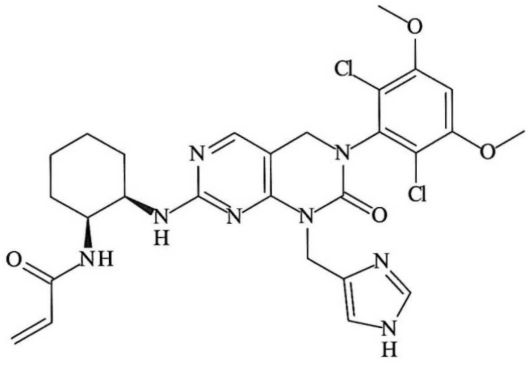

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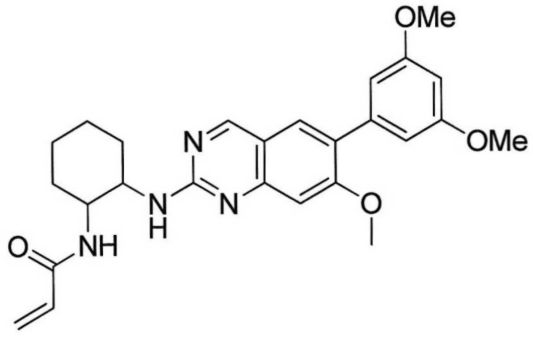

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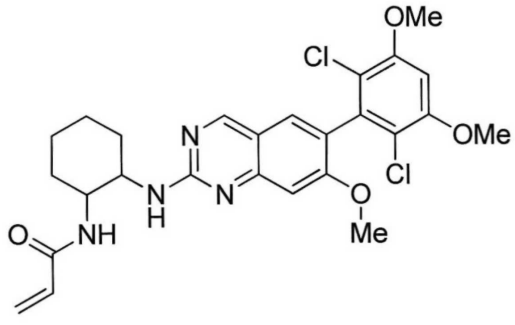

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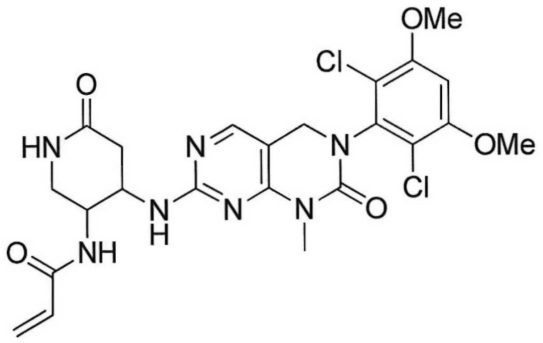

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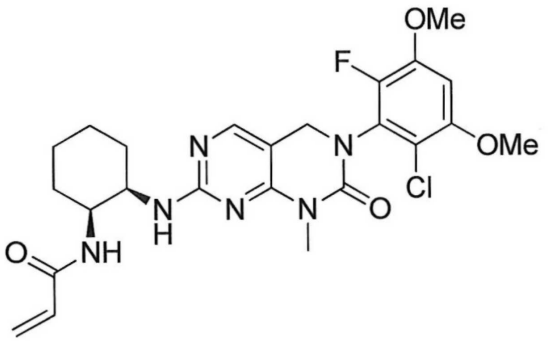

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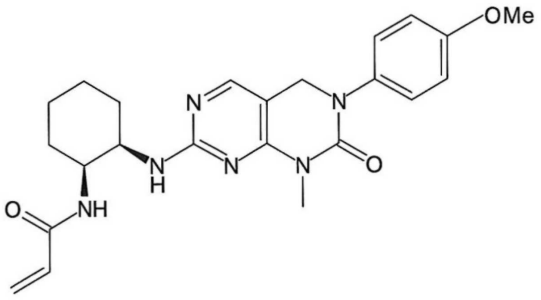

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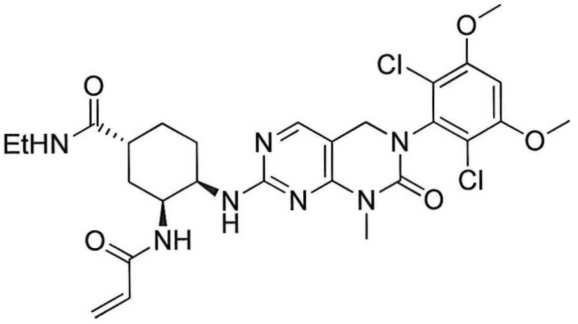

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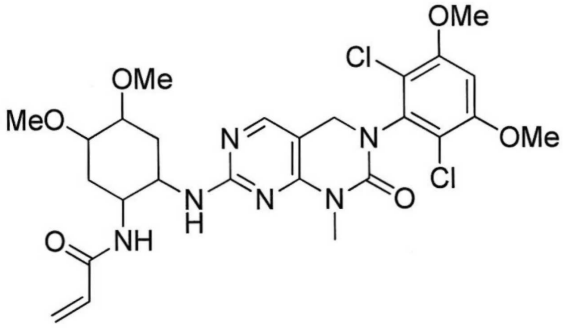

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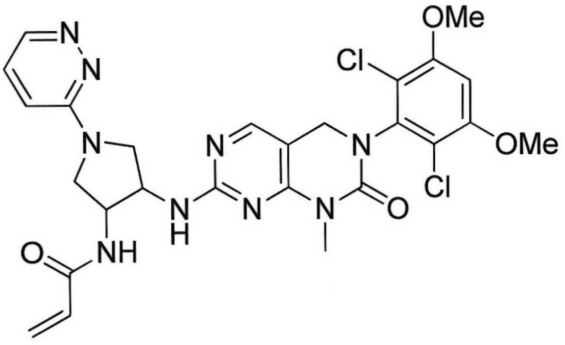

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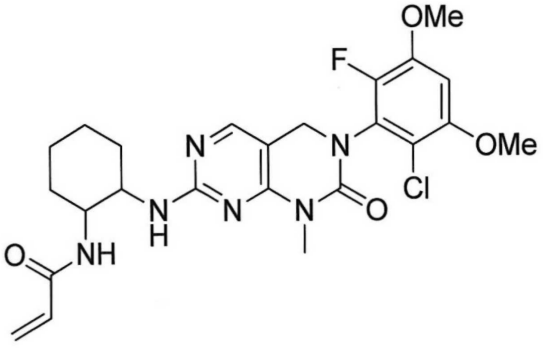

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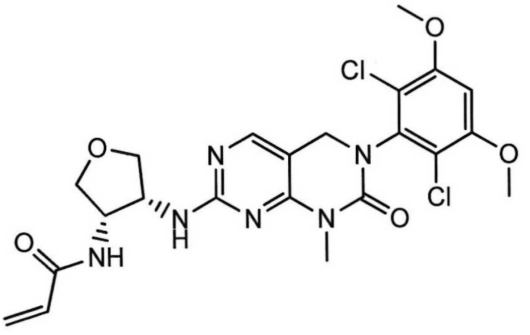

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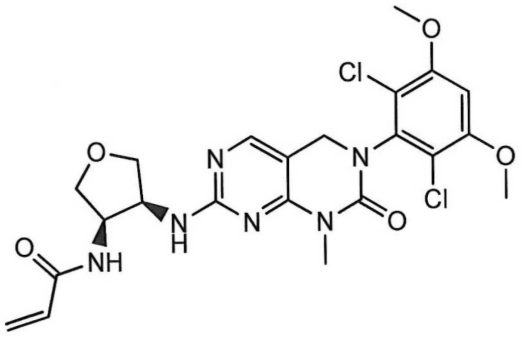

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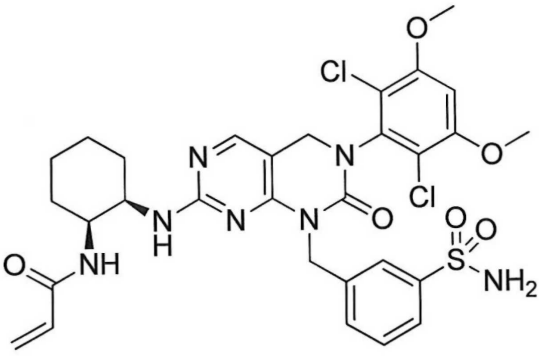

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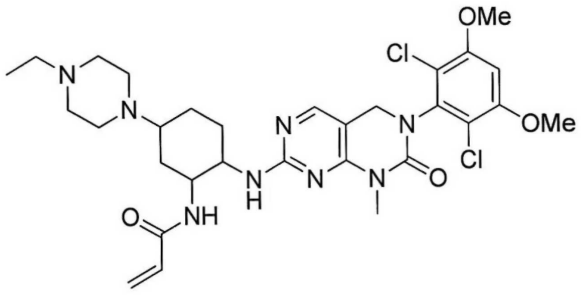

I-191

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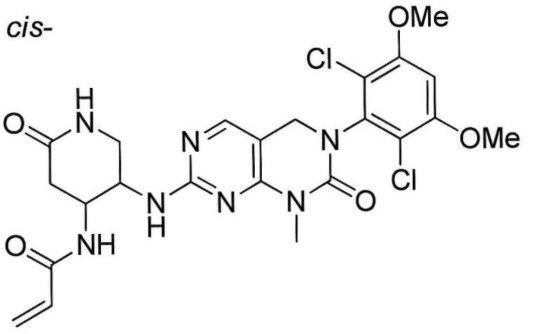

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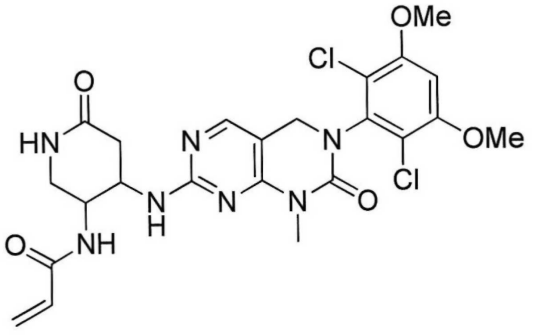

I-194

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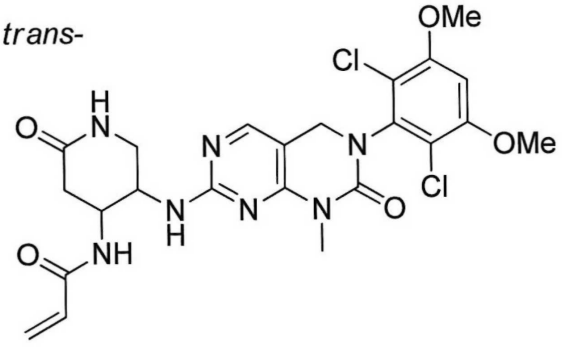

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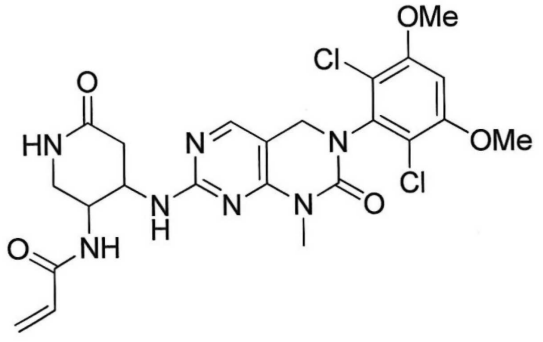

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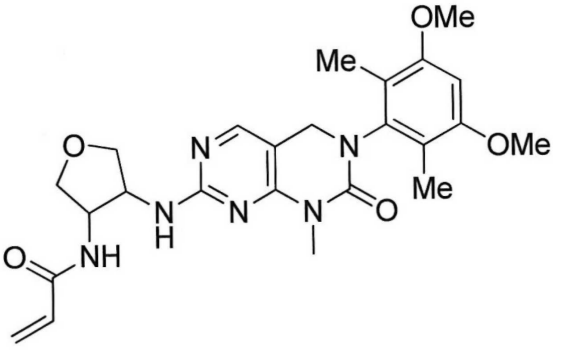

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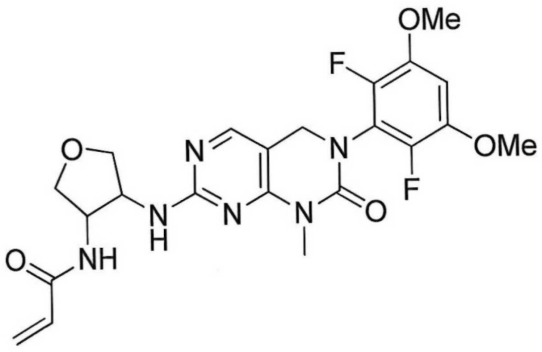

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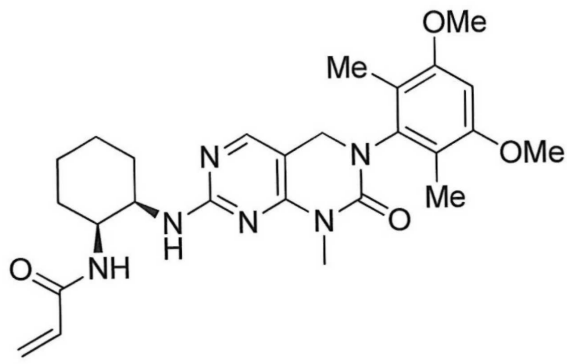

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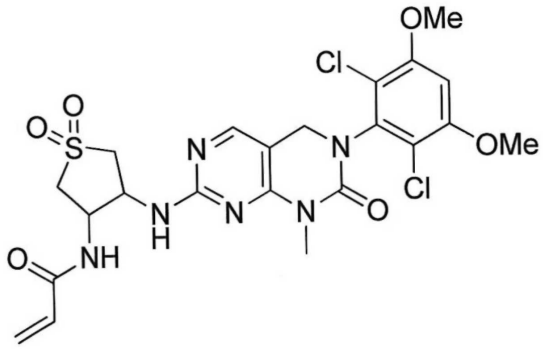

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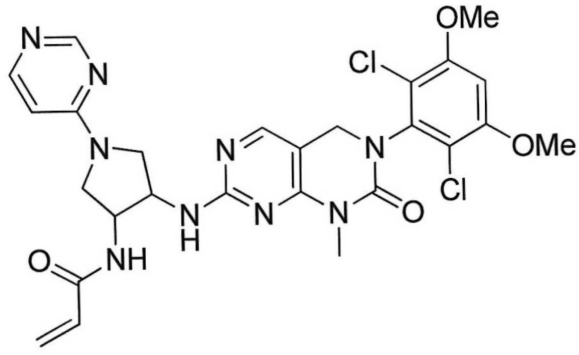

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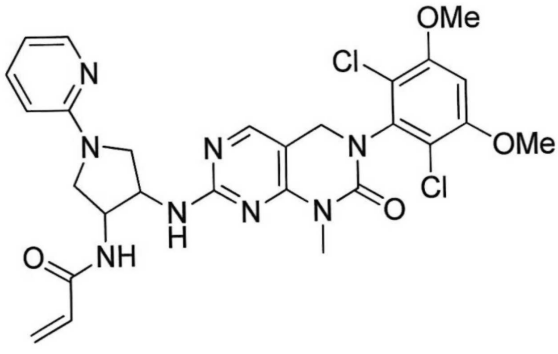

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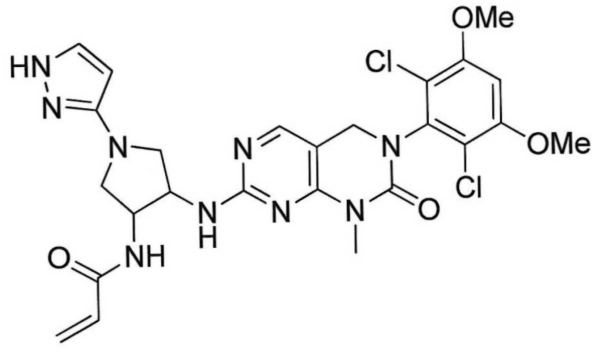

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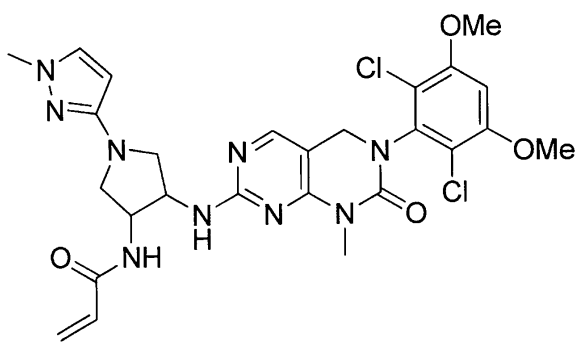

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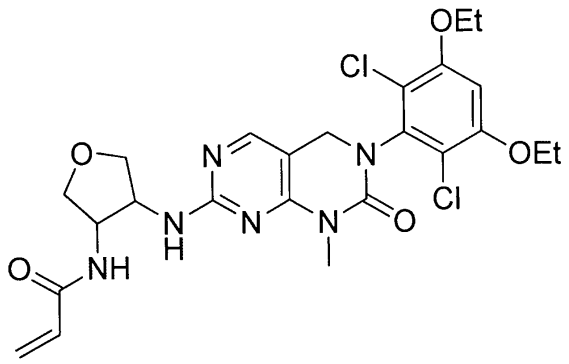

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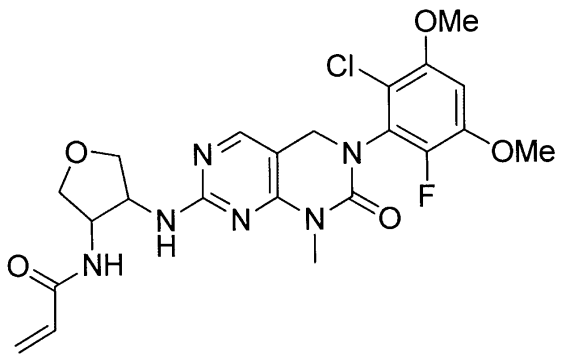

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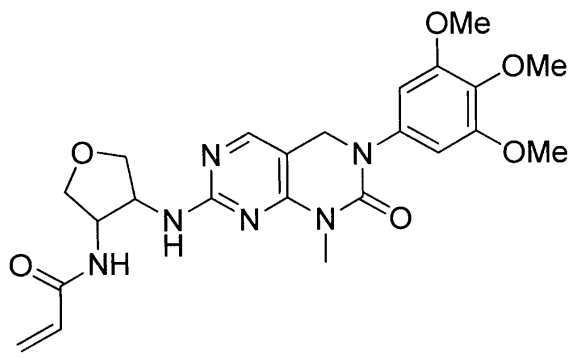

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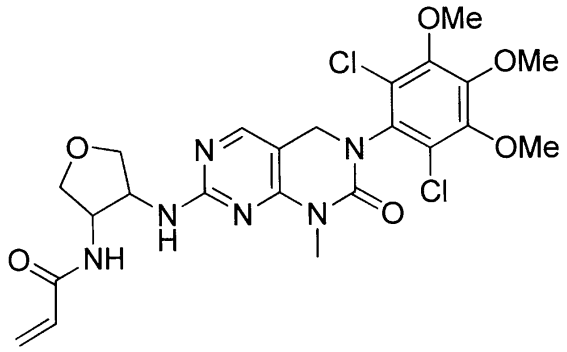

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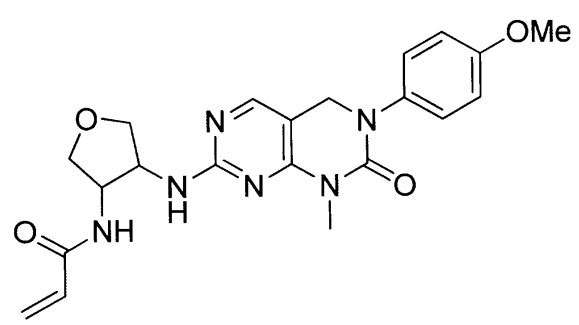

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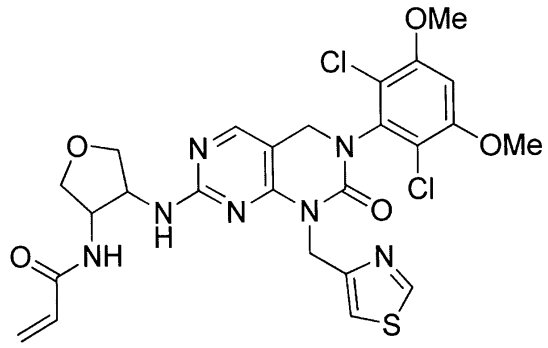

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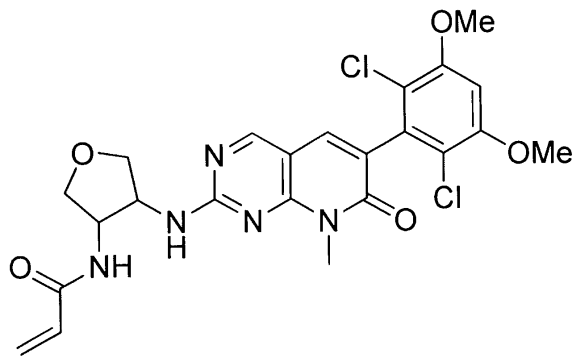

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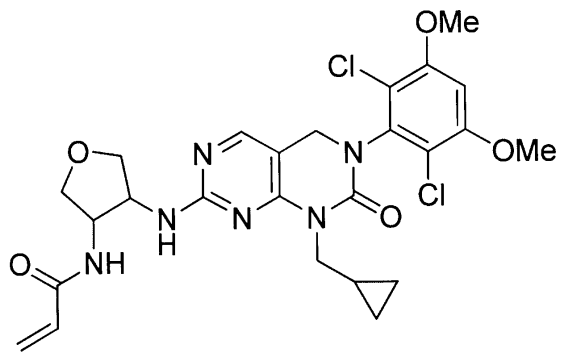

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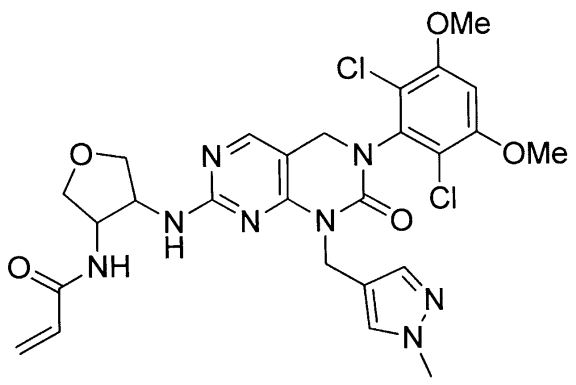

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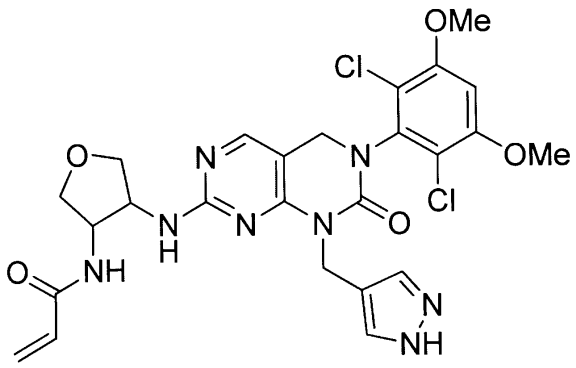

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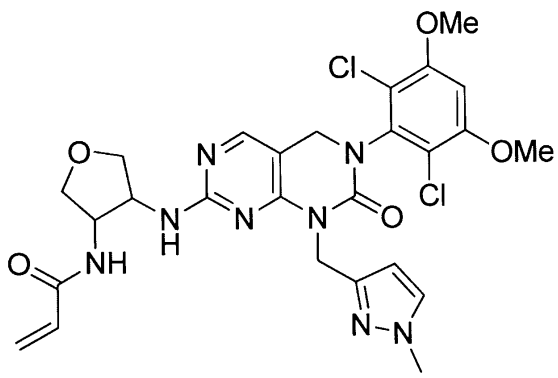

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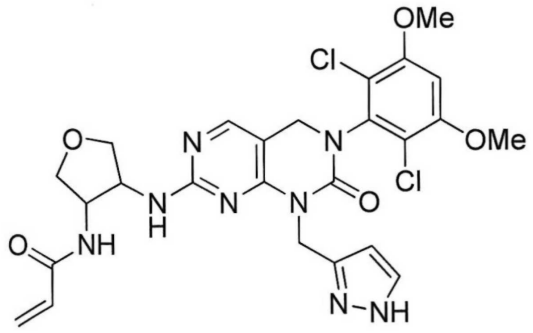

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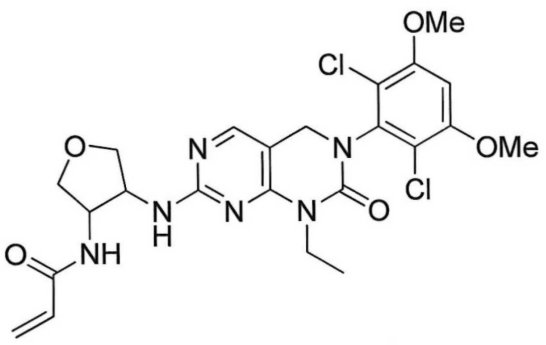

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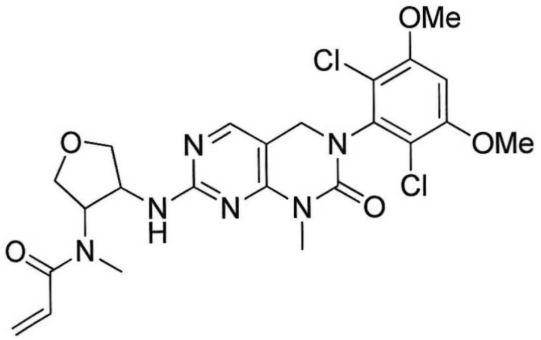

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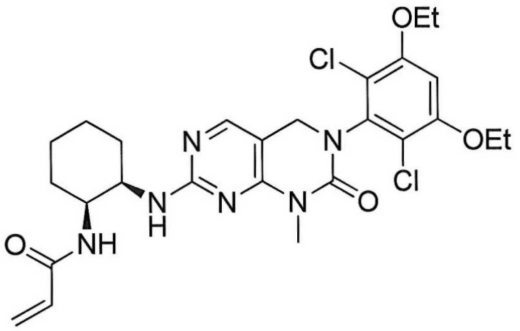

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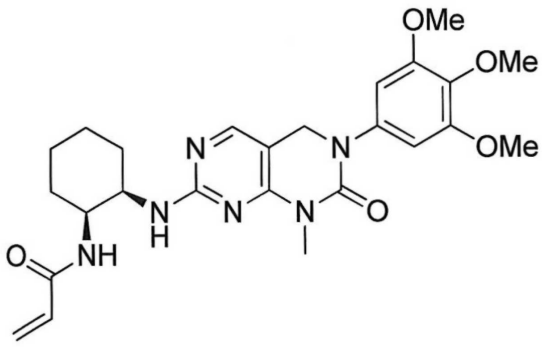

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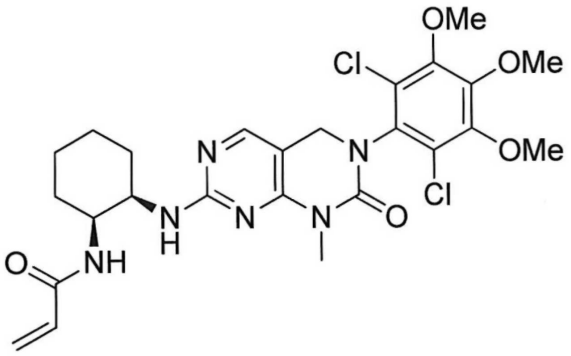

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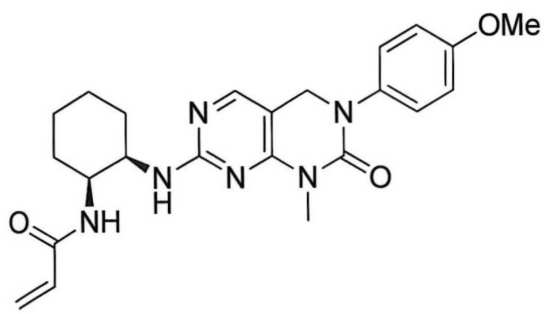

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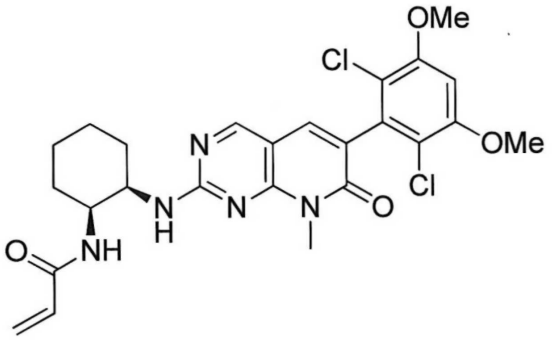

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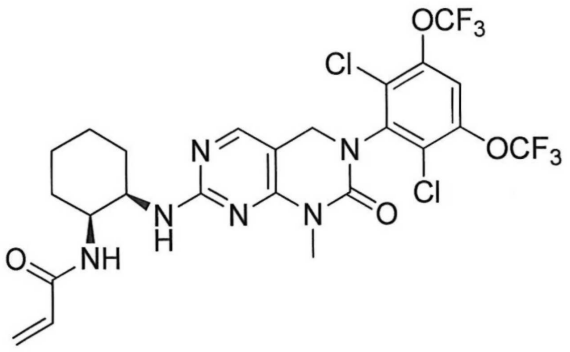

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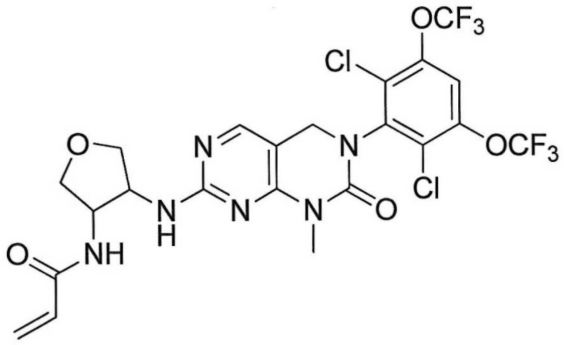

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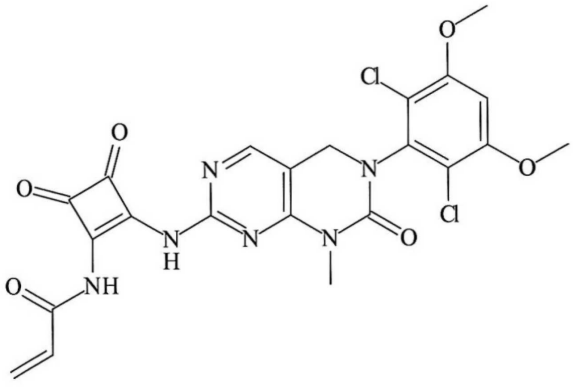

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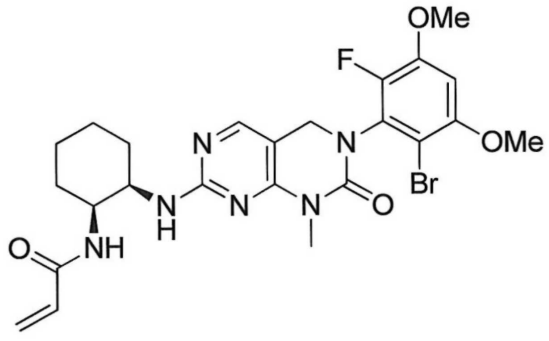

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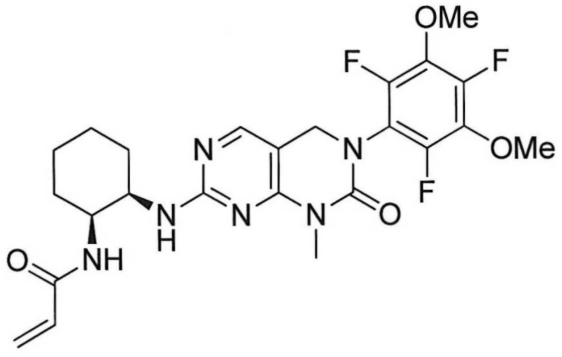

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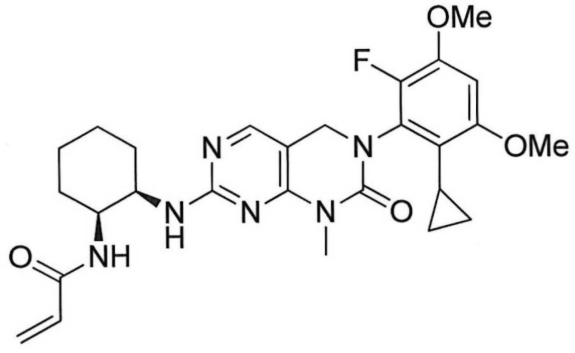

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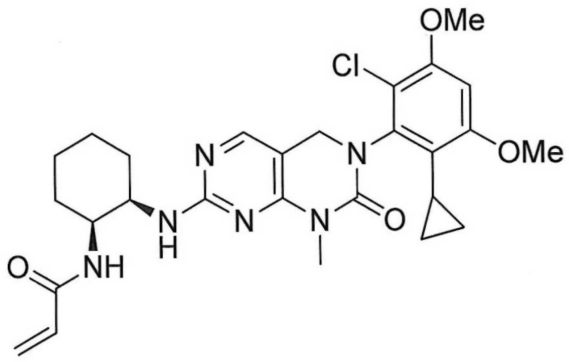

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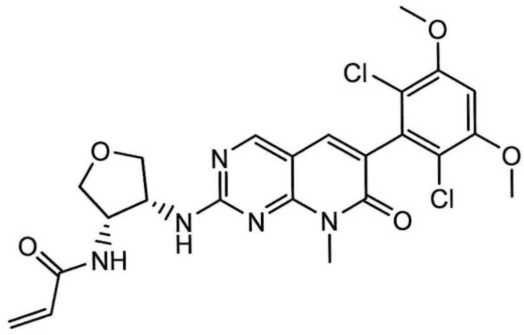

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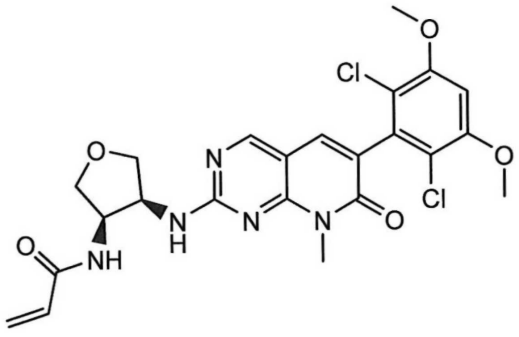

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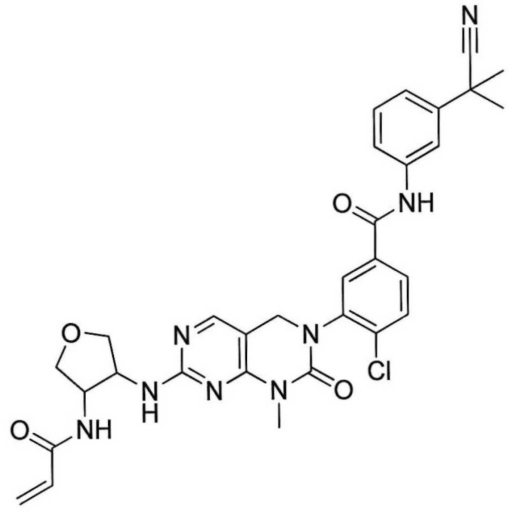

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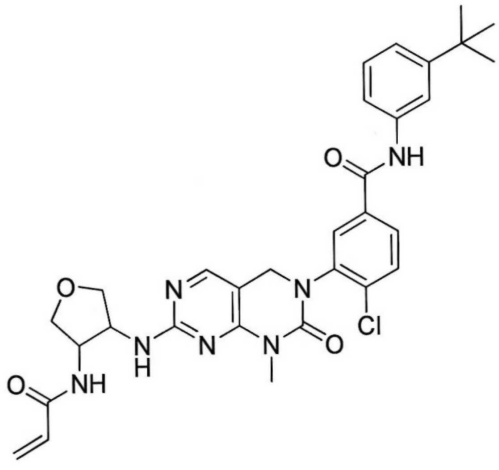

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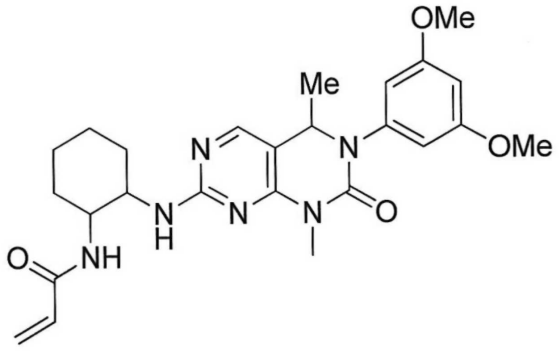
or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 1, selected from



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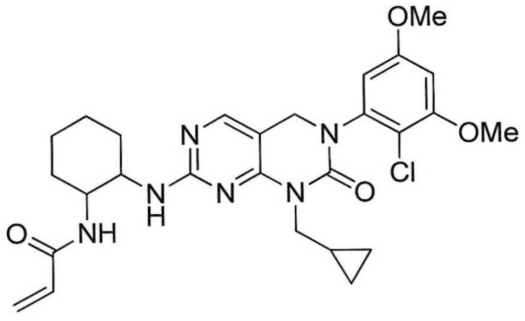

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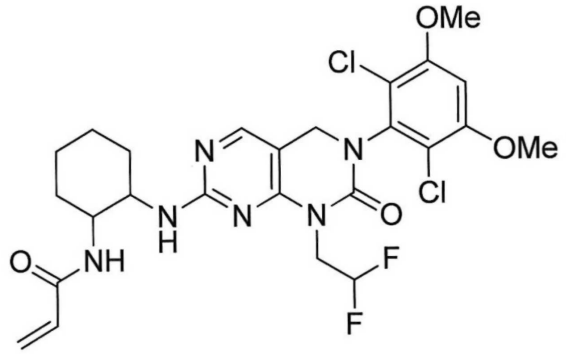

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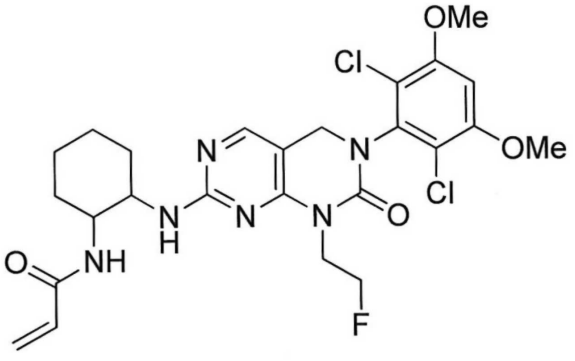

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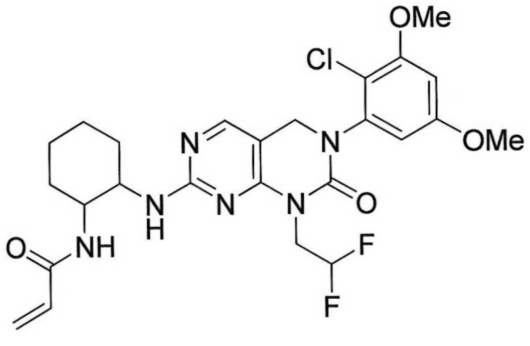

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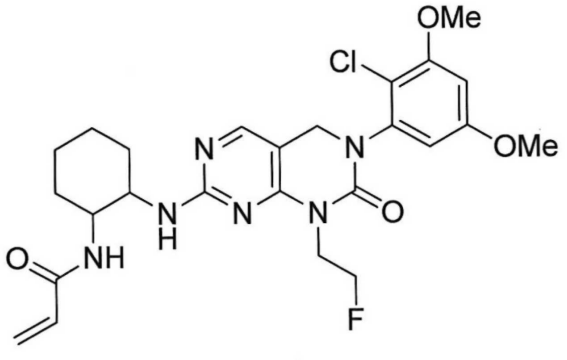

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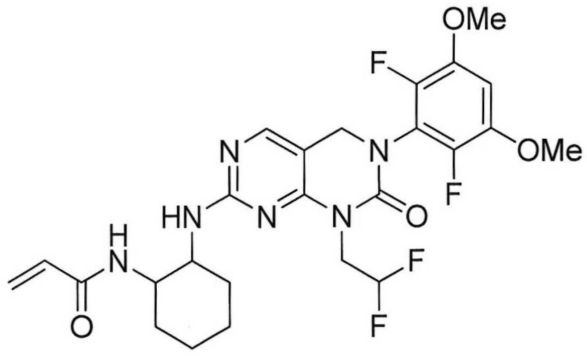

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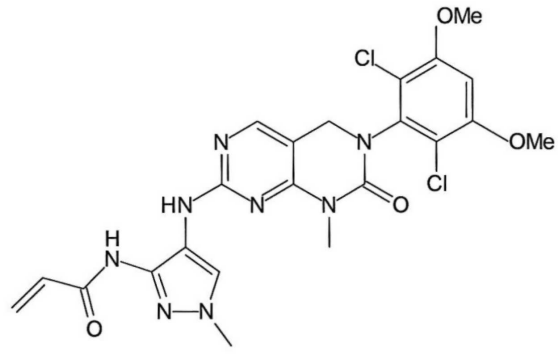

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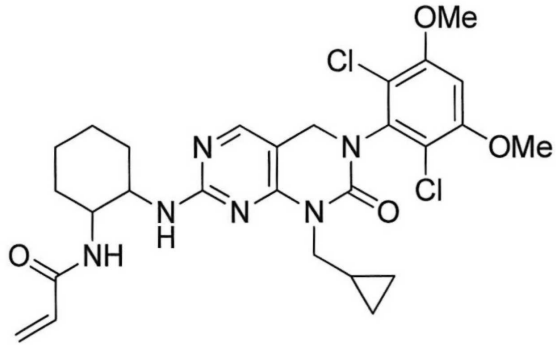

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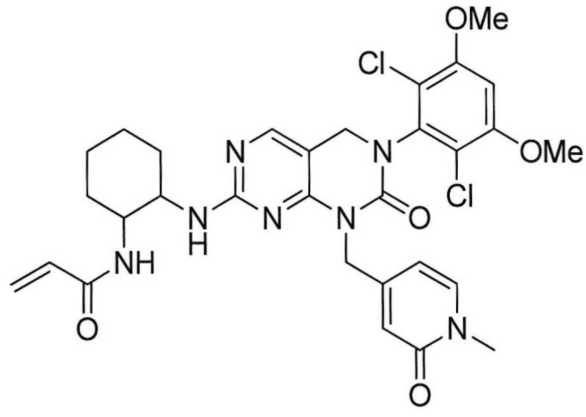

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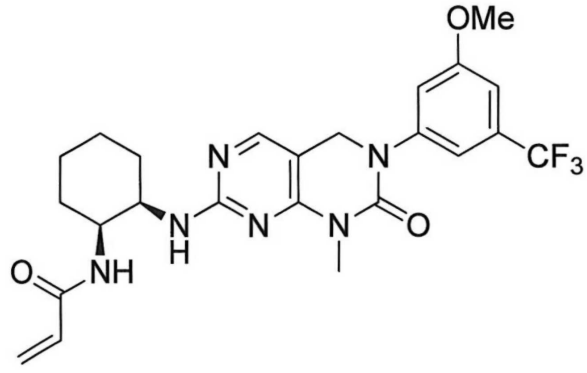

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or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 1, wherein:

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two methylene units of L are optionally and independently replaced

by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, -C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-.

19. The compound according to claim 18, wherein:

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and

the Y group of R^1 is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

20. The compound according to claim 19, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

21. The compound according to claim 19, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -OC(O)-.

22. The compound according to claim 1, wherein L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH_2N(CH_3)-, -NRC(O)CH=CHCH_2O-, -CH_2NRC(O)CH=CH-, -NRSO_2CH=CH-, -NRSO_2CH=CHCH_2-, -NRC(O)C(=CH_2)CH_2-, or -CH_2NRC(O)cyclopropylene-; wherein the R group of L is H or optionally substituted C_{1-6} aliphatic; and the Y group of R^1 is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

23. The compound according to claim 22, wherein L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH_2N(CH_3)-, -NHC(O)CH=CHCH_2O-, -CH_2NHC(O)CH=CH-, -NHSO_2CH=CH-, -NHSO_2CH=CHCH_2-, -NHC(O)C(=CH_2)CH_2-, or -CH_2NHC(O)cyclopropylene-.

24. The compound according to claim 1, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one alkylidenyl double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, -S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

25. The compound according to claim 1, wherein:

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one triple bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or -C(O)O-.

26. The compound according to claim 25, wherein the Y group of R^1 is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

27. The compound according to claim 26, wherein L is -C≡C-, -NHC(O)C≡CCH_2CH_2-, -CH_2-C≡C-CH_2-, or -CH_2OC(=O)C≡C-.

28. The compound according to claim 1, wherein:

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one additional methylene unit of L is replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or -C(O)O-.

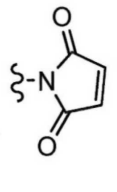
29. The compound according to claim 1, wherein:

L is a covalent bond, -C(O)-, -N(R)C(O)-, or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain.

30. The compound according to claim 1, wherein L is a covalent bond, –CH_2-, -NH-, -C(O)-, -CH_2NH-, -NHCH_2-, –NHC(O)-, -NHC(O)CH_2OC(O)-, -CH_2NHC(O)-, -NHSO_2-, -NHSO_2CH_2-, or -SO_2NH-.

31. The compound according to claim 30, wherein L is a covalent bond.

32. The compound according to claim 1 wherein the Y group of R^1 is selected from:



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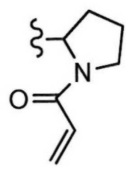

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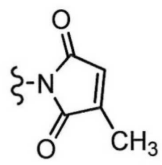

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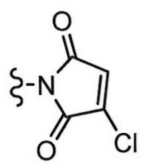

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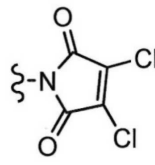

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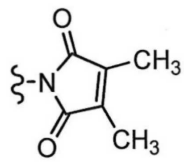

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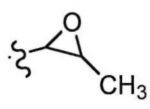

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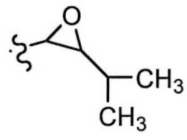

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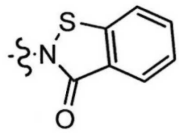

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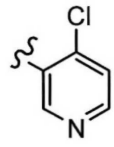

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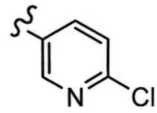

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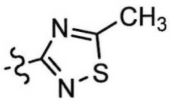

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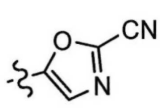

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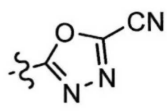

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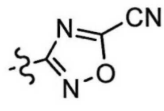

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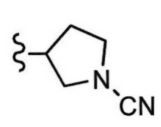

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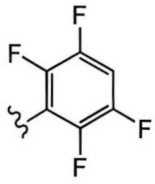

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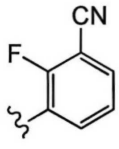

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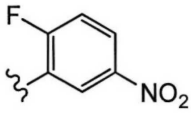

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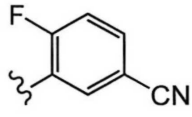

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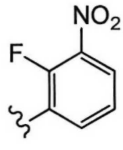

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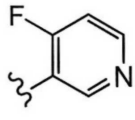

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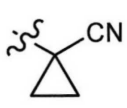

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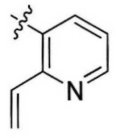

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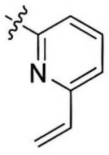

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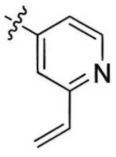

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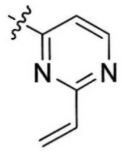

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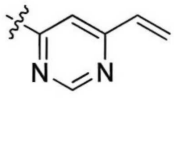

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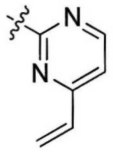

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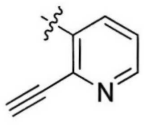

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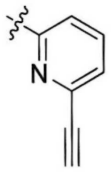

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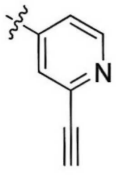

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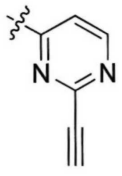

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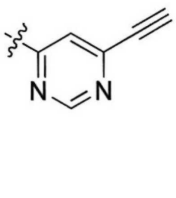

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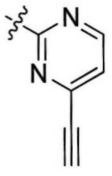

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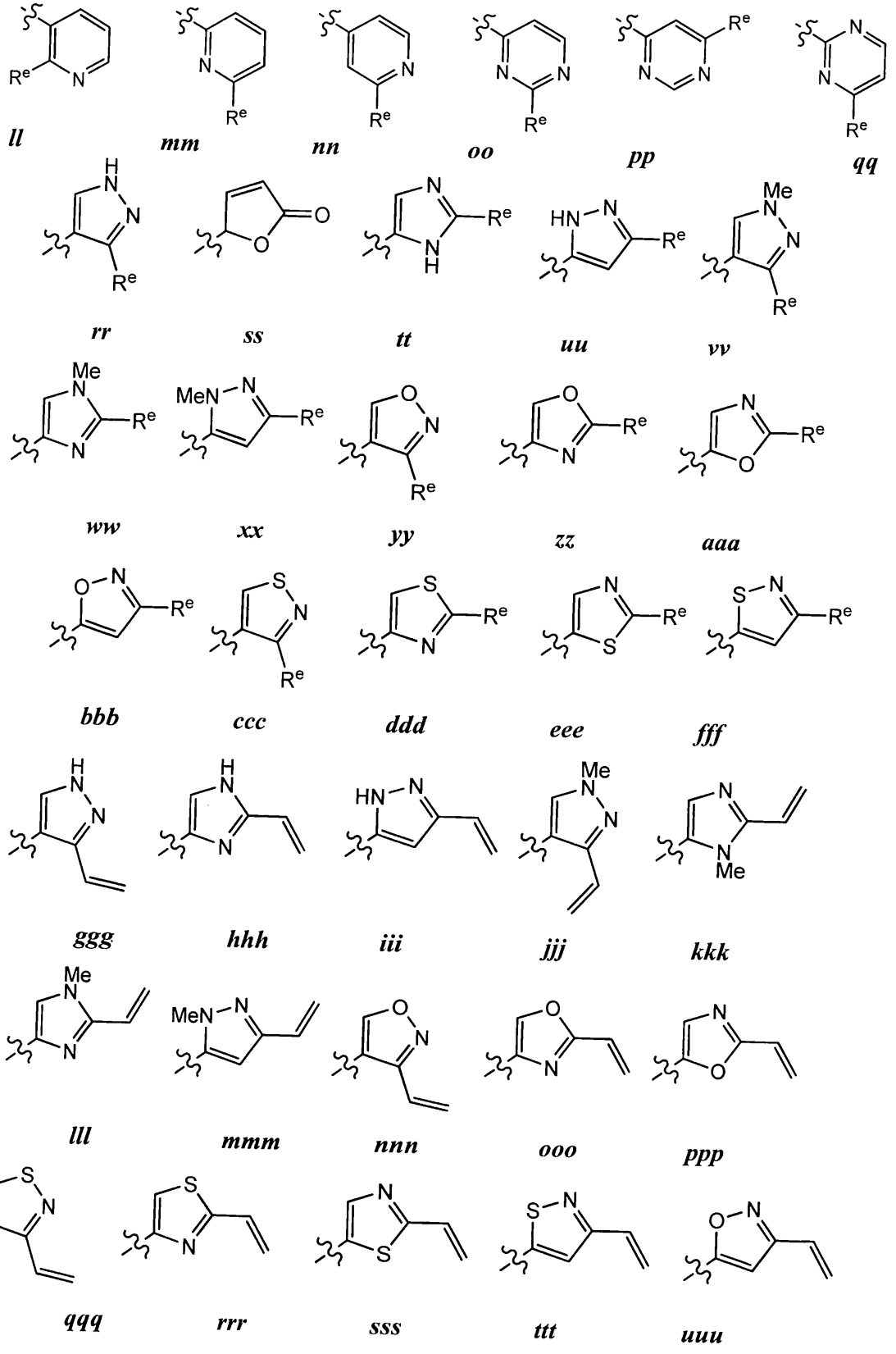
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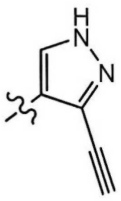

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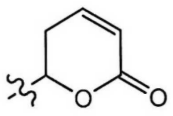

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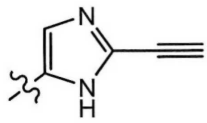

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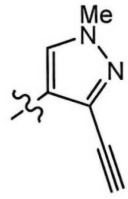

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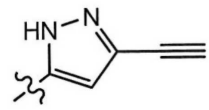

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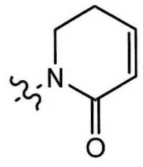

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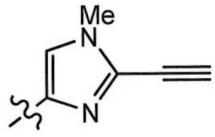

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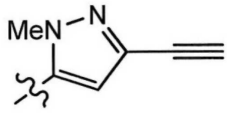

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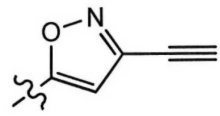

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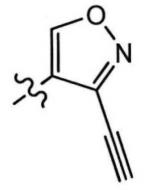

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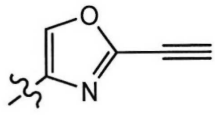

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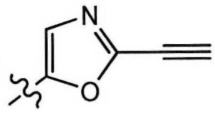

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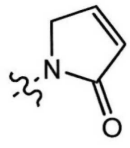

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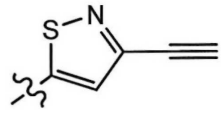

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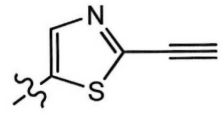

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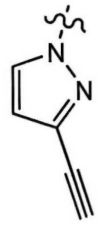

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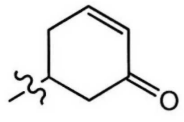

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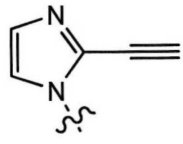

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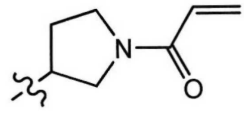

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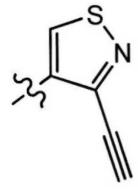

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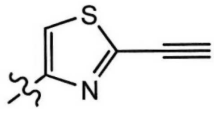

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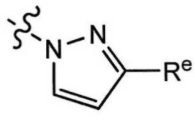

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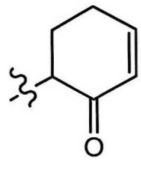

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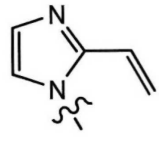

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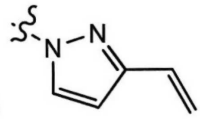

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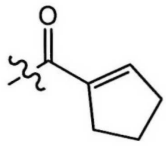

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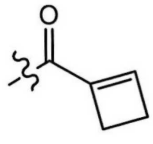

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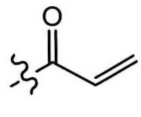

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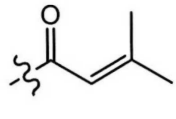

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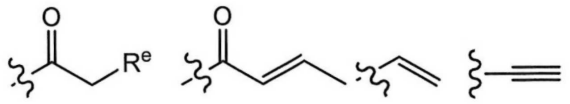
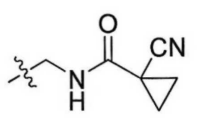


yyyy ***zzzz*** ***bbbbb*** ***ccccc***

wherein each R^e is independently selected from halogen.

33. The compound according to claim 1, wherein R^1 is selected from:



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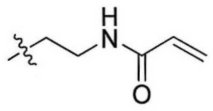

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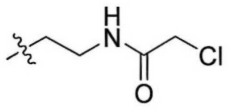

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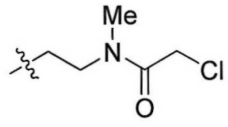

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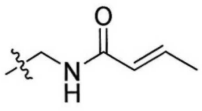

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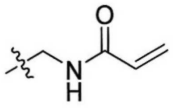

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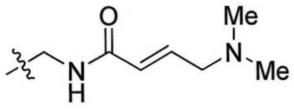

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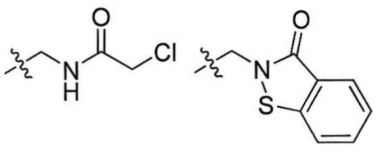

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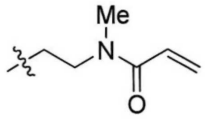

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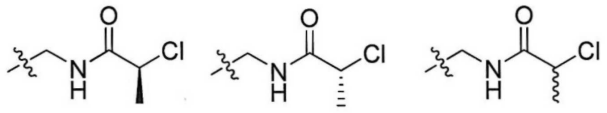

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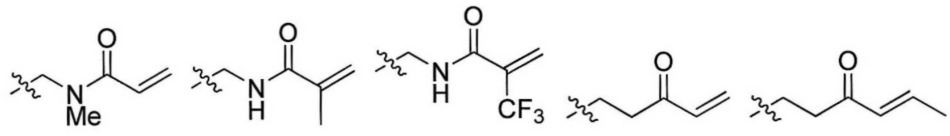

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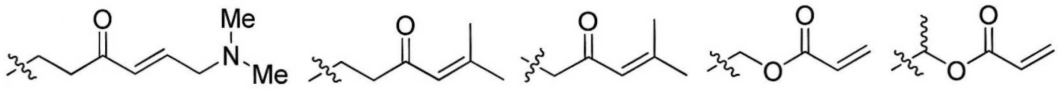

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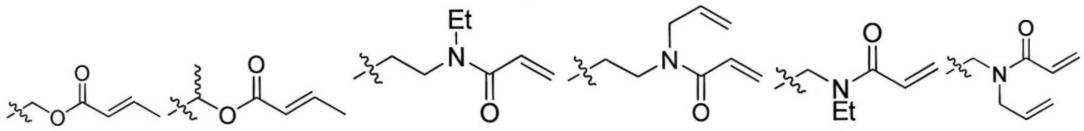

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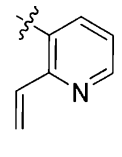

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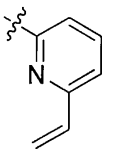

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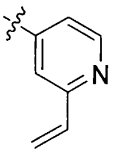

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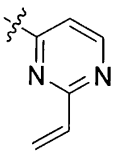

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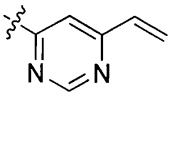

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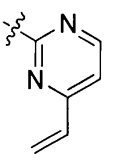

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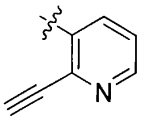

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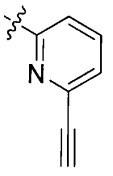

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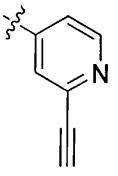

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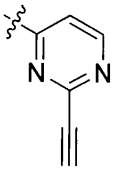

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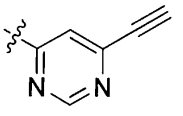

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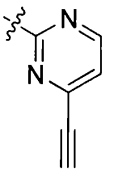

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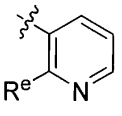

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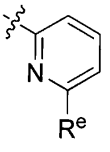

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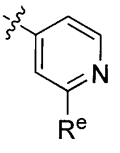

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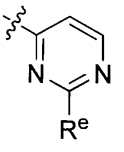

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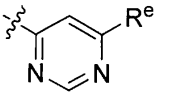

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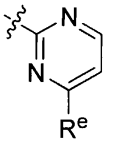

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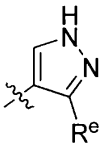

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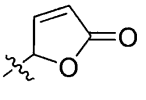

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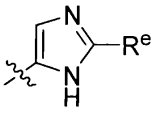

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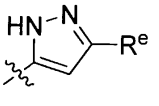

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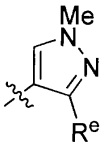

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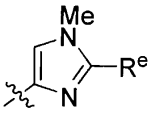

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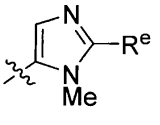

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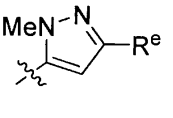

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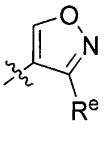

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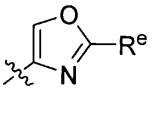

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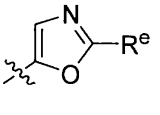

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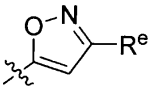

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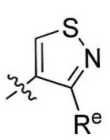

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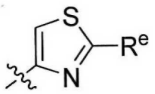

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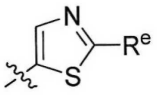

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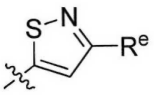

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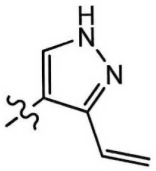

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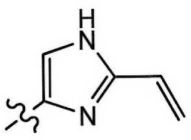

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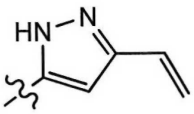

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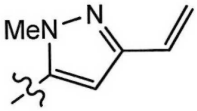

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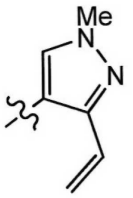

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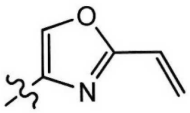

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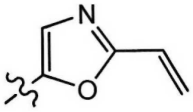

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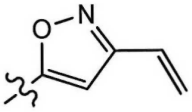

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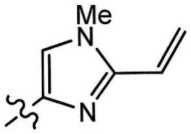

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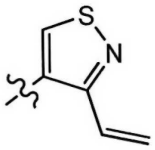

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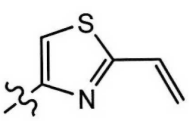

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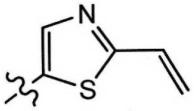

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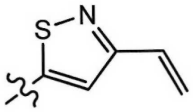

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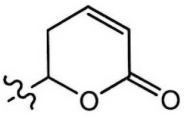

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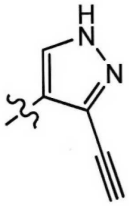

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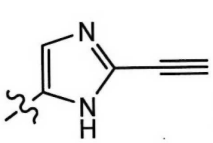

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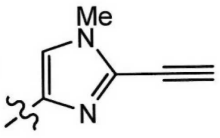

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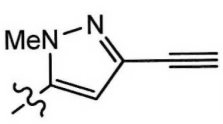

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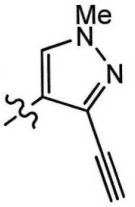

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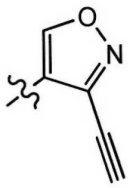

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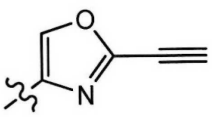

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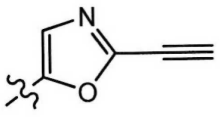

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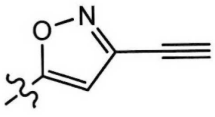

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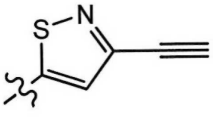

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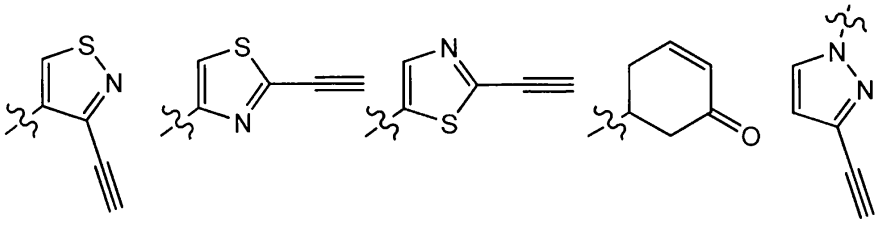
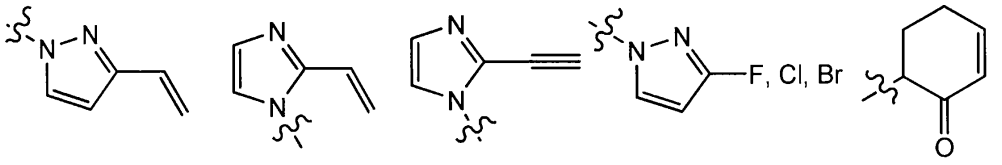
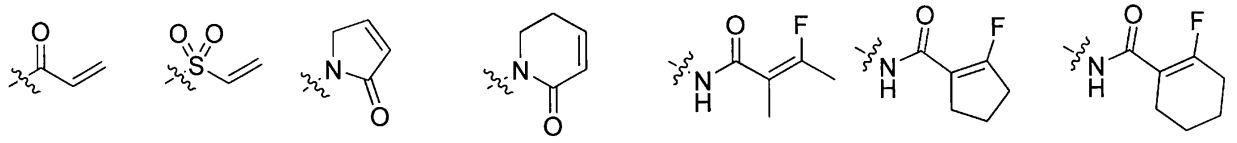


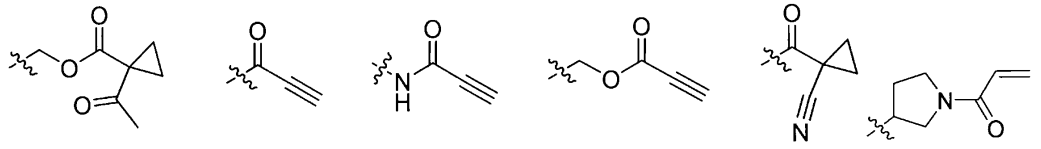
llll *mmmm* *nnnn* *oooo* *pppp*



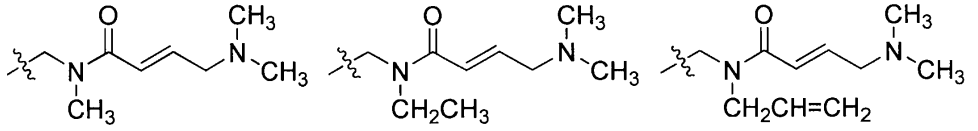
qqqq *rrrr* *ssss* *tttt* *uuuu*



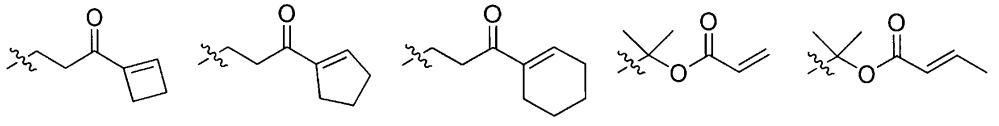
vvvv *wwww* *xxxx* *yyyy* *zzzz* *aaaaa* *bbbbb*



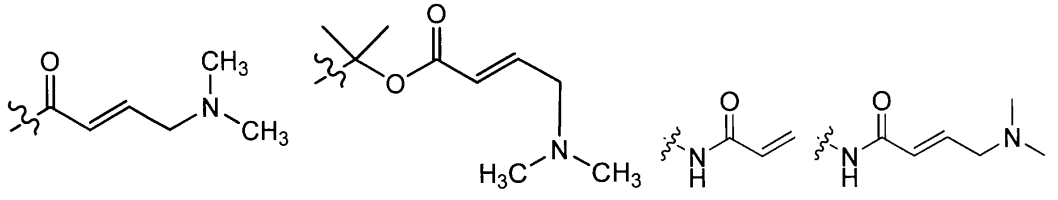
ccccc *ddddd* *eeeee* *fffff* *ggggg* *iiiii*



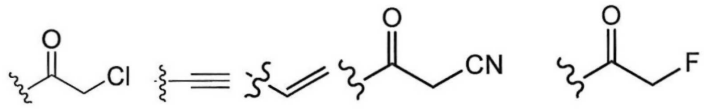
jjjjj *kkkkk* *lllll*



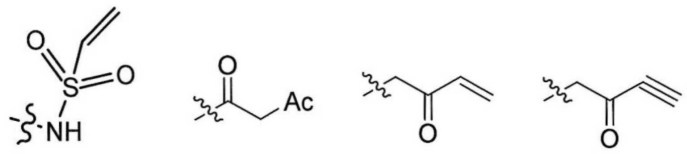
mmmmm *nnnnn* *ooooo* *ppppp* *qqqqq*



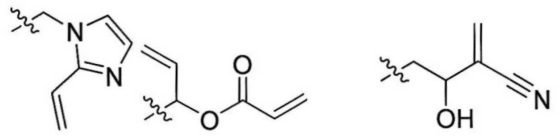
rrrrr *sssss* *ttttt* *uuuuu*



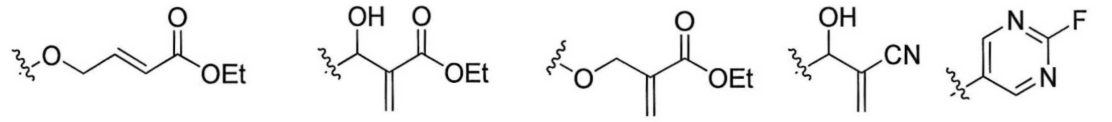
xxxxx ***yyyyy*** ***zzzzz*** ***aaaaaa*** ***bbbbbbb***



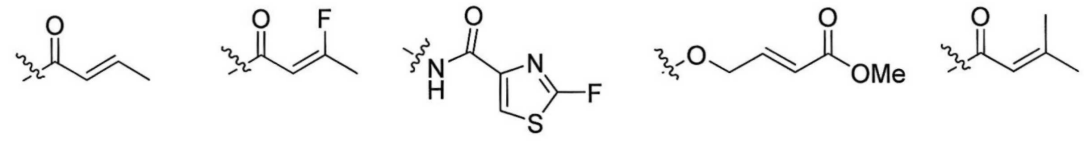
ccccccc ***eeeeee*** ***fffffff*** ***ggggggg***



iiiiii ***kkkkkk*** ***nnnnnn***



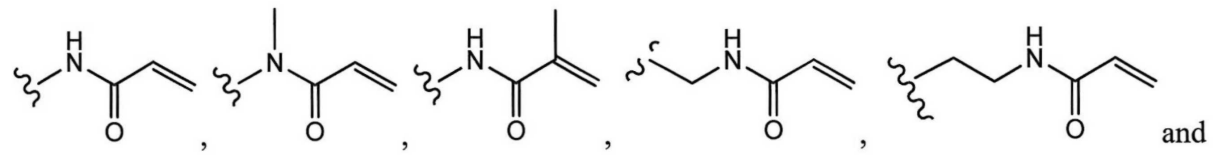
oooooo ***pppppp*** ***qqqqqq*** ***rrrrrr*** ***ssssss***

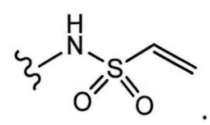


ttttt ***uuuuuu*** ***vvvvvv*** ***wwwwww*** or ***xxxxxx***

wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

34. The compound of claim 1, wherein R^1 is selected from:


and


.

35. A composition comprising a compound according to claim 1, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

36. The compound according to claim 15, wherein:

Ring A is an optionally substituted group selected from a 3-8 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is a warhead group –L-Y; wherein R^1 is attached to an atom adjacent to the atom where T is attached, wherein:

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-; and

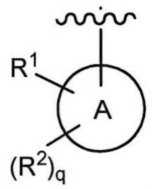
the Y group of R^1 is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with 1-4 R^e groups;

R^3 is C_{1-6} alkyl;

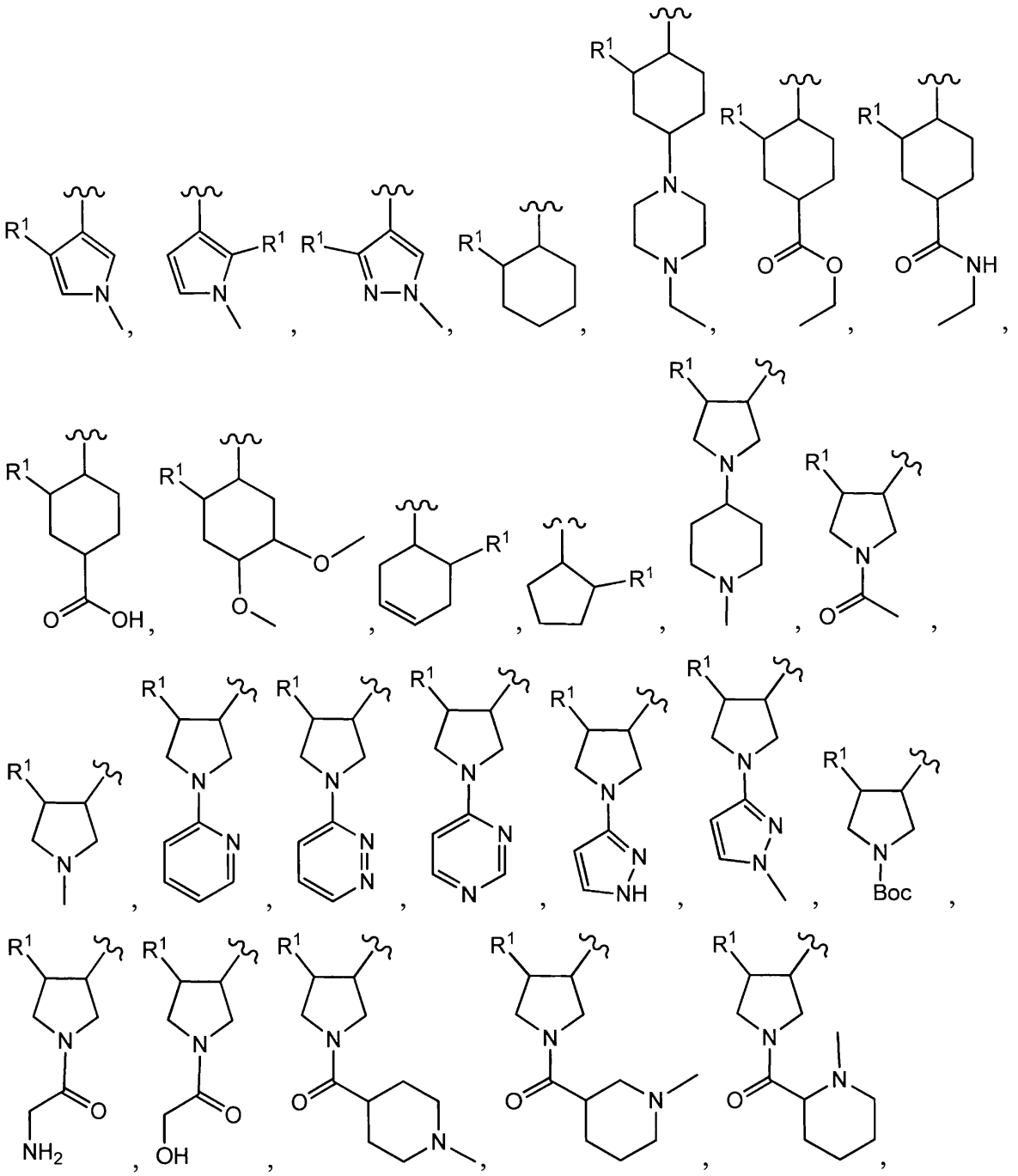
R^4 is optionally substituted phenyl; and

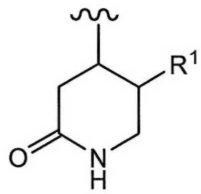
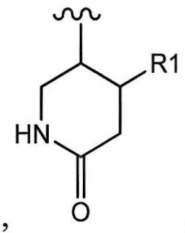
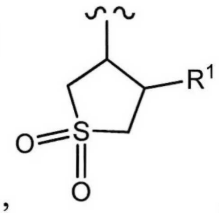
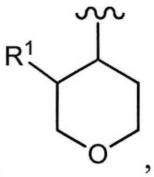
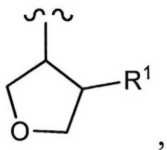
R^a is hydrogen.

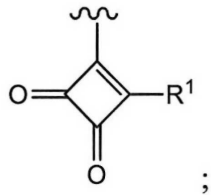
37. The compound according to claim 15, wherein:



is selected from



 ,  ,  ,  ,  , and

 ;

R^1 is a warhead group –L-Y; wherein:

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-; and

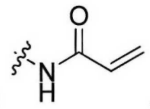
the Y group of R^1 is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with 1-4 R^e groups;

R^3 is C_{1-6} alkyl;

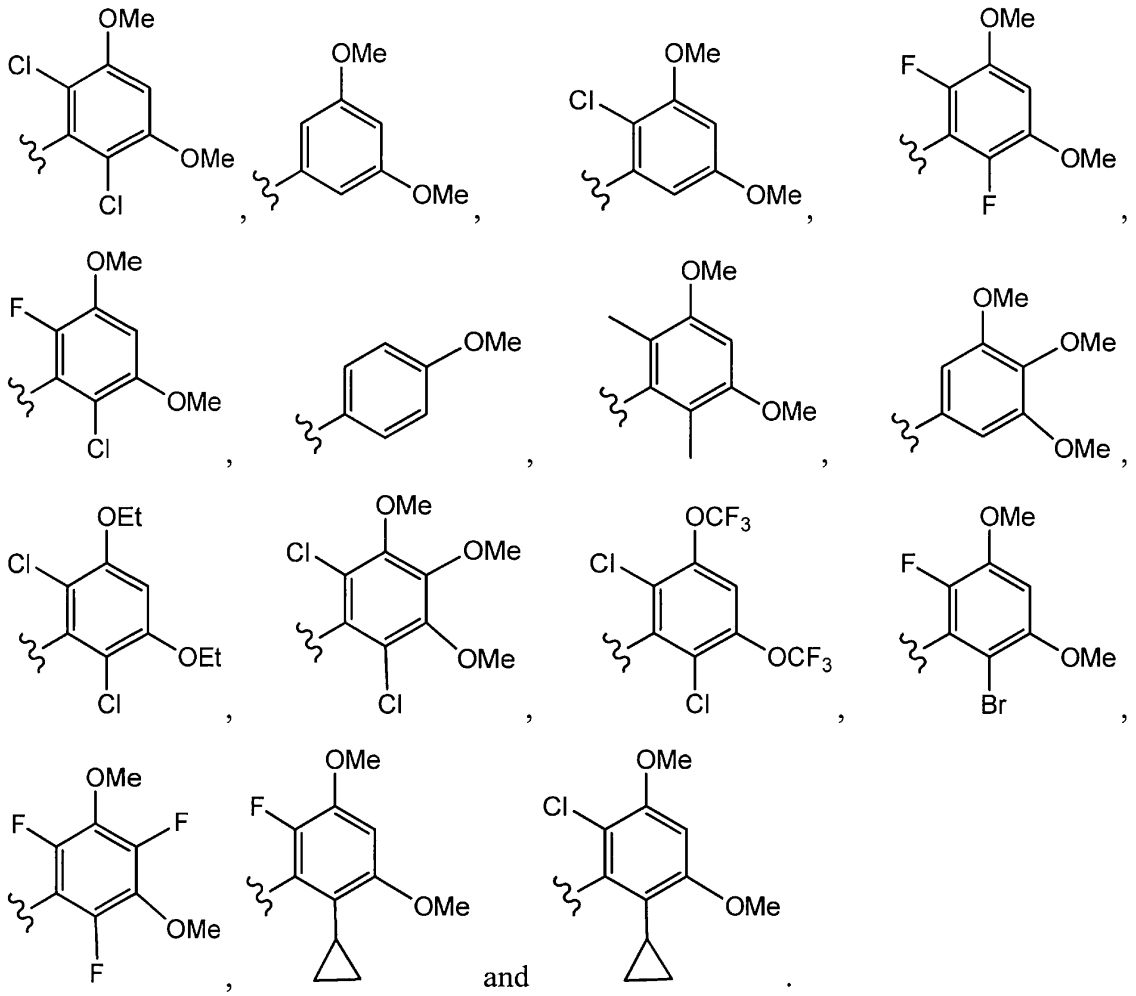
R^4 is optionally substituted phenyl; and

R^a is hydrogen.

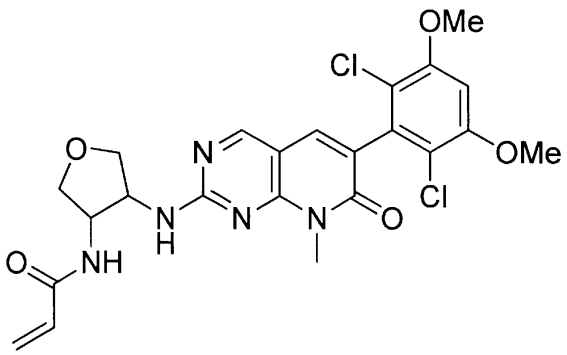
38. The compound according to claim 36, wherein L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH_2N(CH_3)-, -NRC(O)CH=CHCH_2O-, -CH_2NRC(O)CH=CH-, -NRSO_2CH=CH-, -NRSO_2CH=CHCH_2-, -NRC(O)C(=CH_2)CH_2-; wherein the R group of L is H or optionally substituted C_{1-6} aliphatic; and the Y group of R^1 is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

39. The compound according to claim 38, wherein R^1 is  .

40. The compound according to claim 39, wherein R^4 is selected from:



41. The compound according to claim 1 selected from



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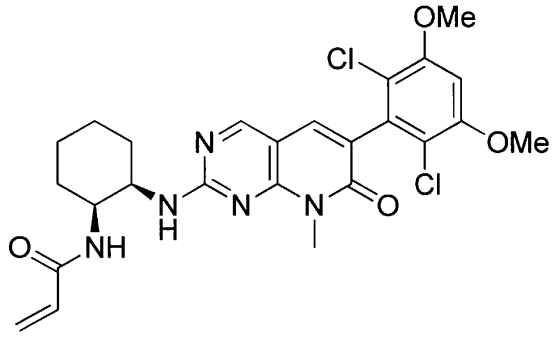

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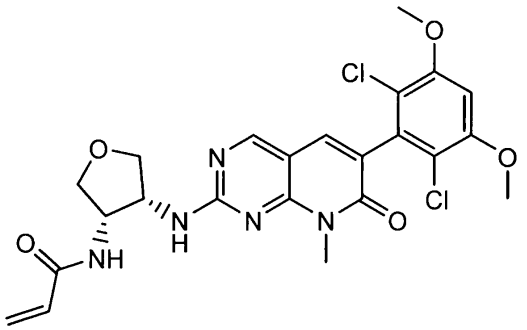
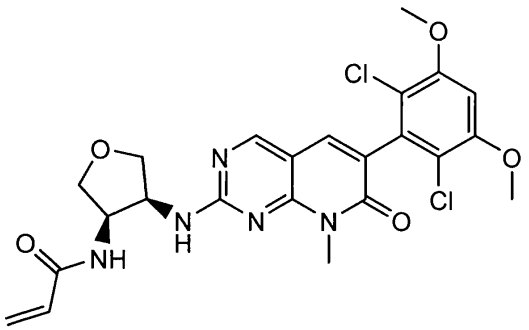


I-240



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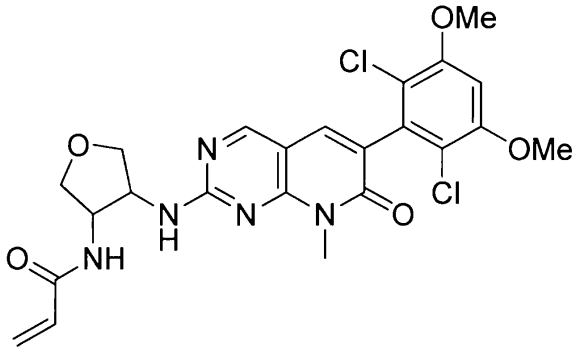
or a pharmaceutically acceptable salt thereof.

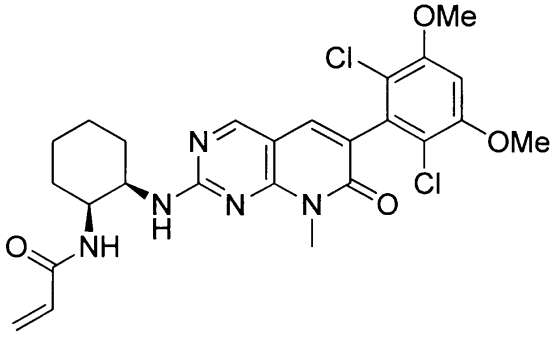
42. The compound according to claim 1, wherein the compound is:



I-211

or a pharmaceutically acceptable salt thereof.

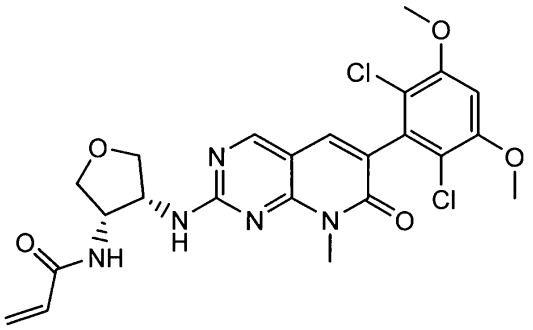
43. The compound according to claim 1, wherein the compound is:



I-223

or a pharmaceutically acceptable salt thereof.

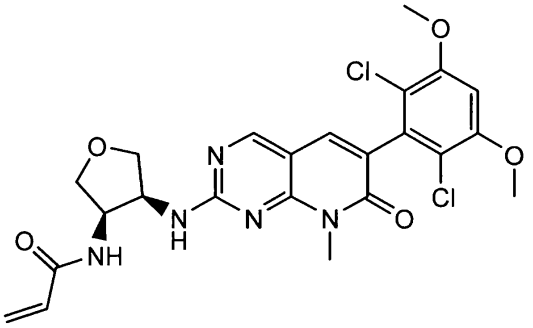
44. The compound according to claim 1, wherein the compound is:



I-240

or a pharmaceutically acceptable salt thereof.

45. The compound according to claim 1, wherein the compound is:



I-241

or a pharmaceutically acceptable salt thereof.

46. A composition comprising a compound according to claim 36, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

47. A composition comprising the compound according to claim 42, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

48. A composition comprising the compound according to claim 43, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

49. A composition comprising the compound according to claim 44, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

50. A composition comprising the compound according to claim 45, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.