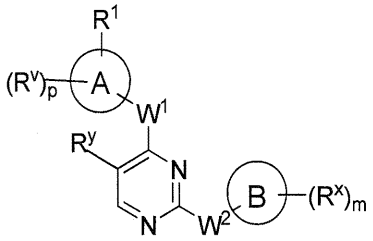
CLAIMS

We claim:

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

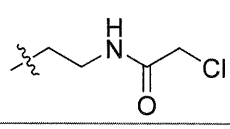
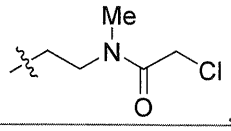
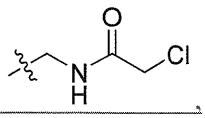
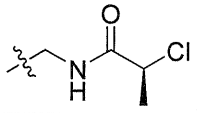
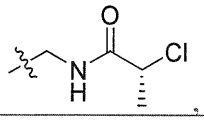
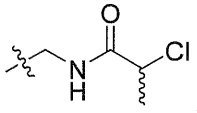
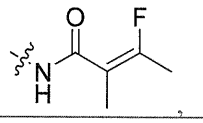
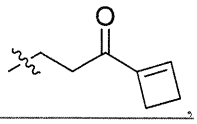
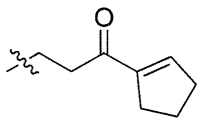
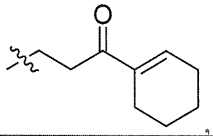
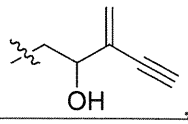
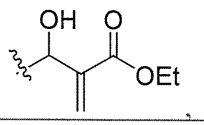
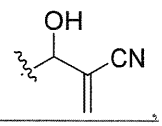
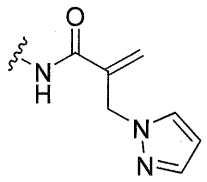
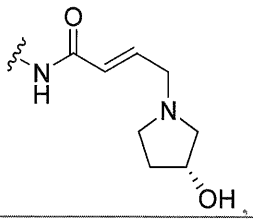
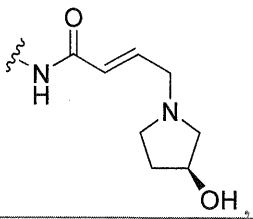
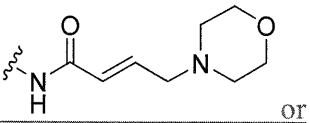
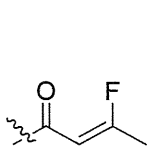
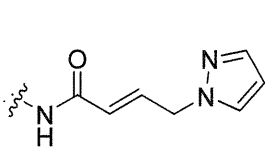
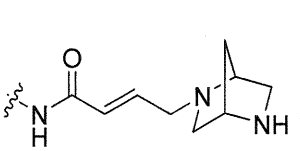
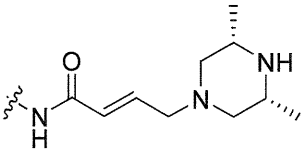


I-b

or a pharmaceutically acceptable salt thereof, wherein:

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

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

R^1 is a warhead group selected from   , , , , , , , , , , , , , ,  or     ; or

R^1 is a warhead group –L-Y selected from the following ~~(a), (b), (c), (h), (k), (l), (m), (n), (o), and (p)~~ combinations of –L- and –Y, ~~and~~ wherein R^1 is attached to an atom other than an atom adjacent to the atom attached to W^1 on Formula **I-b**:

~~(a)~~ L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two ~~additional~~ 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 Y is ~~hydrogen or~~ 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, wherein said ring is substituted with 1-4 R^e groups; or

~~(b)~~ 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 or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; ~~and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN;~~ or

~~(c)~~ 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 or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; ~~and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN;~~ or

~~(h)~~ 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 or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; ~~and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN;~~ and

Y 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

~~(k) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one or two additional methylene units of L are 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 Y C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or~~

~~(l)~~ L is a covalent bond and Y is ~~selected from:~~ C_{2-6} alkenyl substituted with oxo, halogen, NO_2, or CN; or

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

~~(*ii*) C_{2-6} alkenyl 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~~

~~(*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~~

~~(*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~~

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

~~(*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;~~

~~(m)~~ L is –C(O)- or –N(R)C(O)- and Y 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~~

(*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

(*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

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

(*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;

(n) L is $N(R)C(O)$- and Y 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

(*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

(*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

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

(*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;

(o) L is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and Y is selected from:

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

(*ii*) C_{2-6} alkenyl 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

(*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

(*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

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

~~(p)~~ L is ~~a covalent bond,~~ CH_2-, -NH-, -C(O)-, $-CH_2NH$-, $-NHCH_2$-, –NHC(O)-, $-NHC(O)CH_2OC(O)$-, $-CH_2NHC(O)$-, $-NHSO_2$-, $-NHSO_2CH_2$-, ~~$-NHC(O)CH_2OC(O)$-~~, or $-SO_2NH$-; and Y 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

~~(*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~~

~~(*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~~

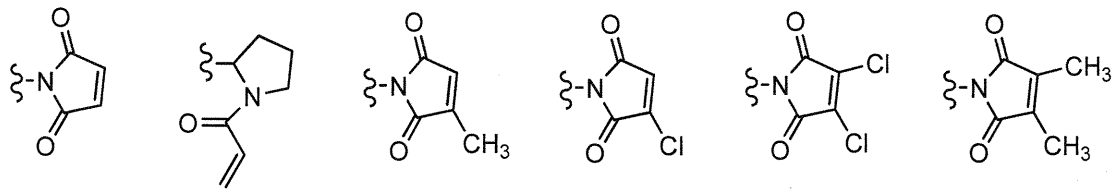
~~(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or~~

~~(*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~~

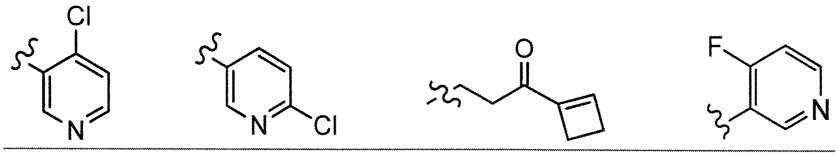
~~(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or~~

~~(*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;~~

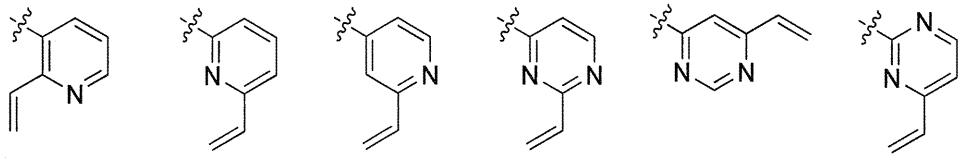
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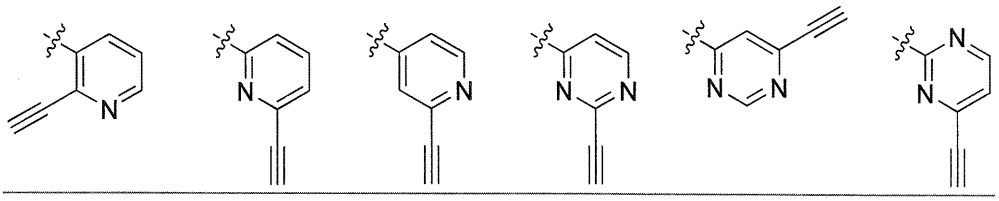
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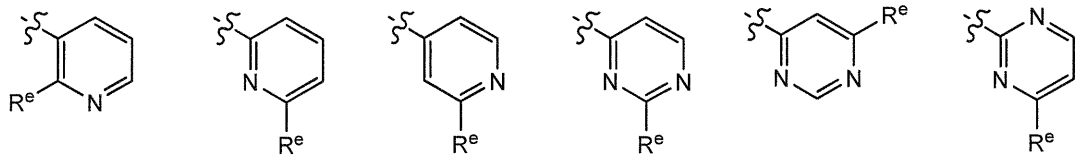
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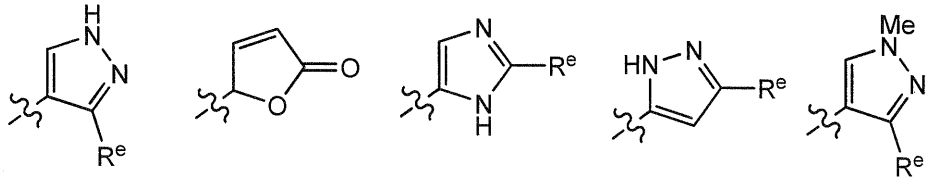
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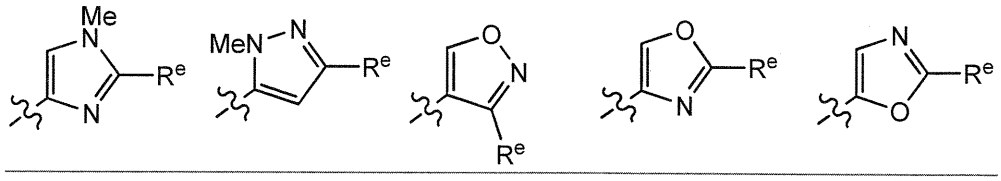
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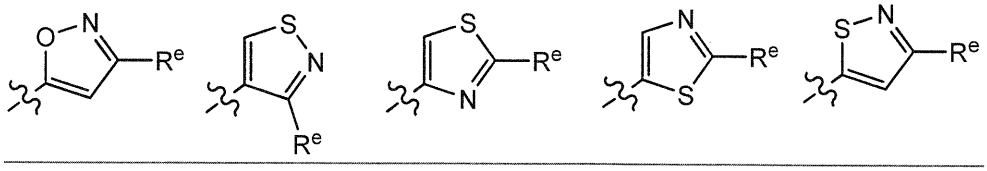
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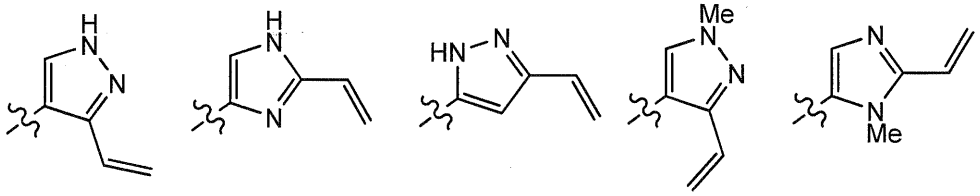
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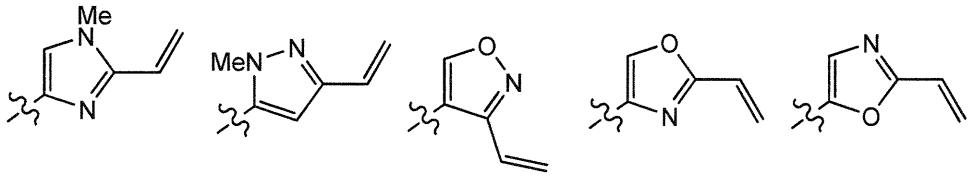
ww *xx* *yy* *zz* *aaa*



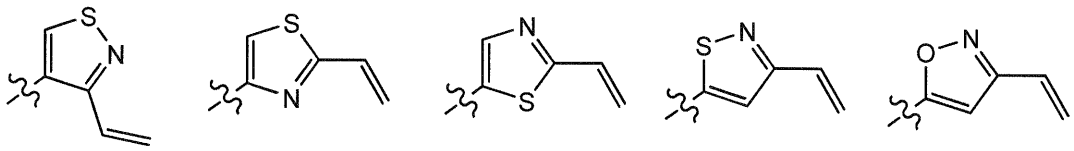
bbb *ccc* *ddd* *eee* *fff*



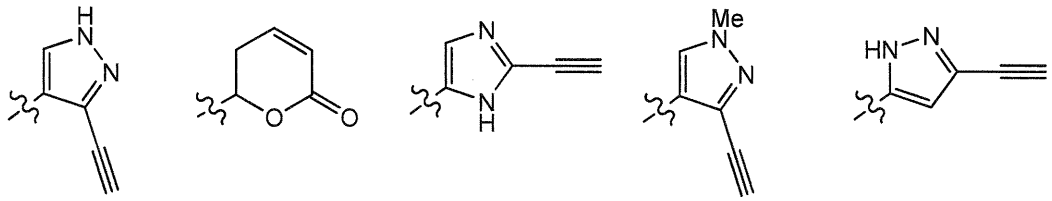
ggg *hhh* *iii* *jjj* *kkk*



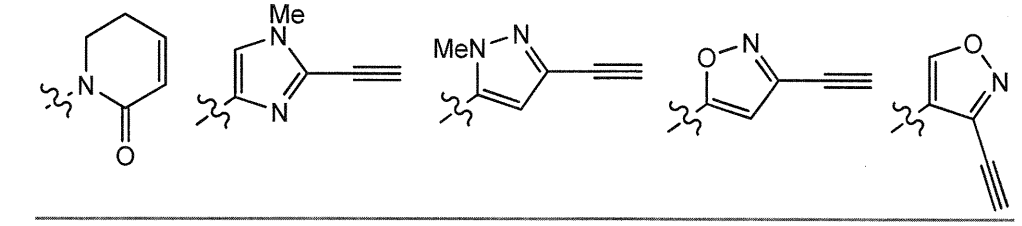
lll *mmm* *nnn* *ooo* *ppp*



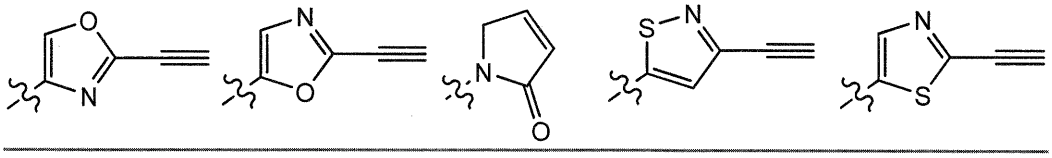
qqq *rrr* *sss* *ttt* *uuu*



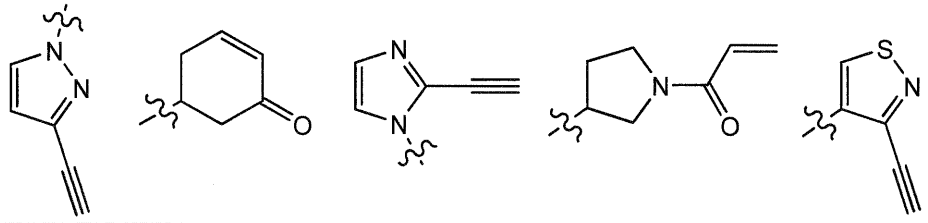
vvv *qqq* *www* *xxx* *yyy*



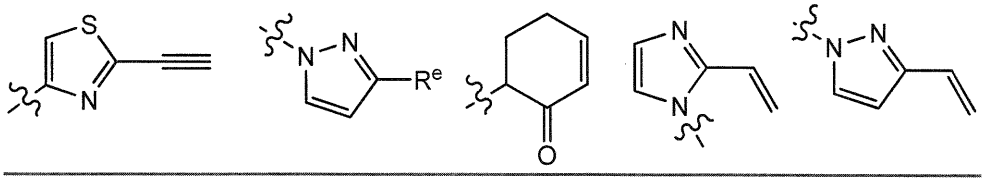
zzz *aaaa* *bbbb* *cccc* *dddd*



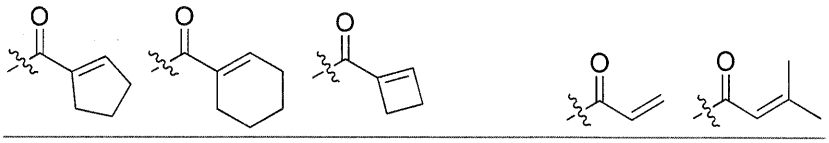
eeee *ffff* *gggg* *hhhh* *iiii*



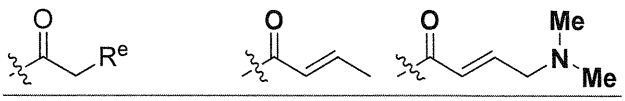
jjjj *kkkk* *llll* *mmmm* *nnnn*



oooo *pppp* *qqqq* *rrrr* *ssss*



tttt *uuuu* *vvvv* *wwww* *xxxx*



yyyy *zzzz* *aaaaa*

each R^e is independently selected from –Q-Z, oxo, NO_2, halogen, CN, a suitable leaving group selected from alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy,

optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, diazonium, or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, 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;

R^y is ~~halogen,~~ -CN, -CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, -OR, -C(O)R, or -C(O)N($R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocylic 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;

W^1 and W^2 are each -NR^2-;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R~~, or:~~

~~R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or~~

~~R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;~~

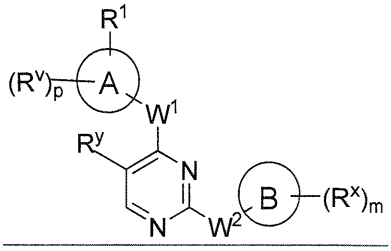
m and p are independently 0-4;~~ and~~

each instance of R^x is independently selected from –R, -OR, -O($CH_2)_q$OR, or halogen, wherein q is 1-4; and

each instance of R^v is independently selected from -R, halogen, –OR, -O($CH_2)_q$OR, –CN, –NO_2, -SO_2R, -SO_2N($R)_2$, -SOR, -C(O)R, -CO_2R, –C(O)N($R)_2$, -NRC(O)R, -NRC(O)N($R)_2$, -NRSO_2R, or -N($R)_2$, wherein q is 1-4 ~~; or:~~

~~R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, CN, or C_{1-6} aliphatic.~~

2. A compound of formula **I-b**:



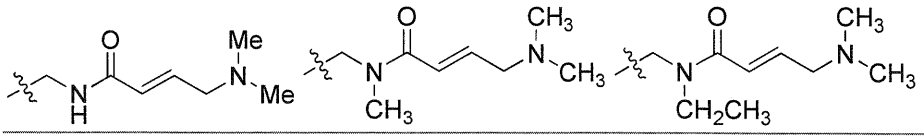
I-b

or a pharmaceutically acceptable salt thereof, wherein:

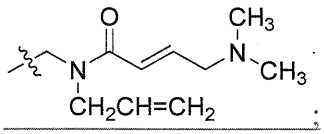
Ring A is optionally substituted phenyl;

Ring B is optionally substituted phenyl;

R^1 is a warhead group –L-Y, or R^1 is selected from:



and



;

wherein R^1 is attached to Ring A at a position other than an atom adjacent to the atom attached to W^1;

L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH$_2$N(CH$_3$)-, -NRC(O)CH=CHCH$_2$O-, -NRSO$_2$CH=CH- , -NRSO$_2$CH=CHCH$_2$-, -NRC(O)(C=N$_2$)-, -NRC(O)(C=N$_2$)C(O)-, -NRC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NRC(O)-, -CH$_2$NRC(O)CH=CH-, -CH$_2$CH$_2$NRC(O)-, -CH$_2$NRC(O)cyclopropylene-, -C(O)CH=C(CH$_3$)-, -C(O)CH=CHCH$_2$NH(CH$_3$)-, –C(O)CH=CH-, -CH$_2$C(O)CH=CH-, -CH$_2$C(O)CH=C(CH$_3$)-, -CH$_2$CH$_2$C(O)CH=CH-, -CH$_2$CH$_2$C(O)CH=CHCH$_2$-, -CH$_2$CH$_2$C(O)CH=CHCH$_2$N(CH$_3$)-, -CH$_2$CH$_2$C(O)CH=C(CH$_3$)-, –CH(CH$_3$)OC(O)CH=CH-, –CH$_2$OC(O)CH=CHCH$_2$–, -CH$_2$-OC(O)CH=CH– or -CH(CH=CH$_2$)OC(O)CH=CH–; wherein R is H or optionally substituted C$_{1-6}$ aliphatic; and Y is hydrogen or C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN;

R^y is hydrogen, halogen, -CN, -CF$_3$, C$_{1-4}$ aliphatic, C$_{1-4}$ haloaliphatic, -OR, -C(O)R, or -C(O)N(R)$_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 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;

W^1 is –O-;

W^2 is $-NR^2-$;

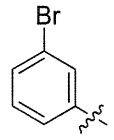
R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R;

m and p are independently 0, 1, 2, 3 or 4;

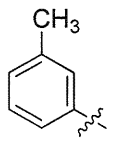
R^x is selected from -R, halogen, –OR, $-O(CH_2)_qOR$, $-NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1, 2, 3 or 4; and

R^v is selected from -R, halogen, –OR, $-O(CH_2)_qOR$, –CN, $-NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1, 2, 3 or 4.

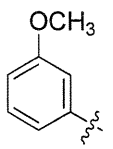
~~23~~. The compound according to claim 1 or claim 2, wherein Ring A is selected from:



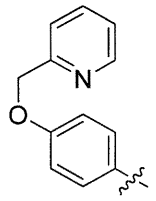
i



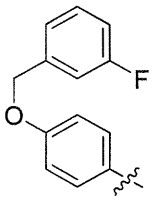
ii



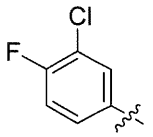
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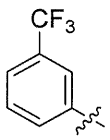
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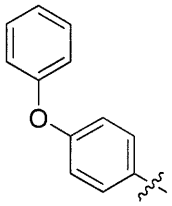
vi



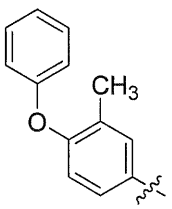
vii



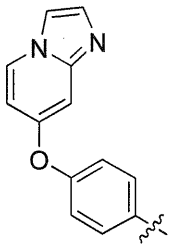
viii



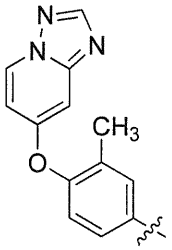
ix



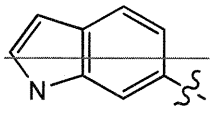
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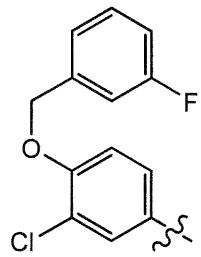


xi

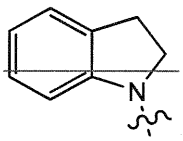


xii

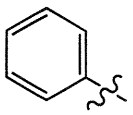




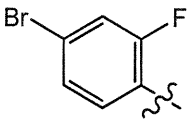
~~*xiii*~~ *xiv*



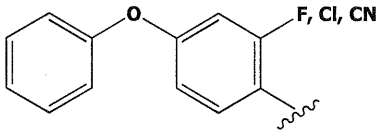
~~*xv*~~



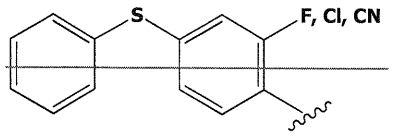
xvi



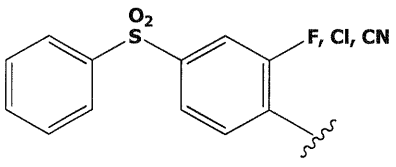
xvii



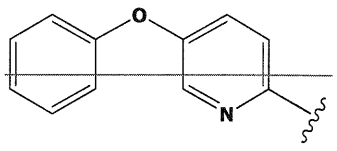
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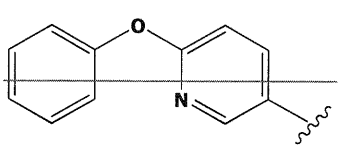


~~*xix*~~

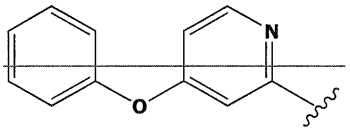


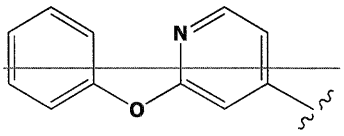
xx

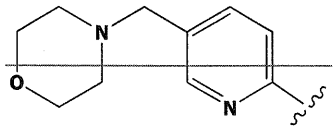




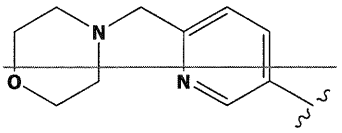
~~*xxi*~~ ~~*xxii*~~

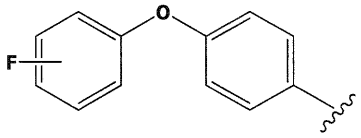


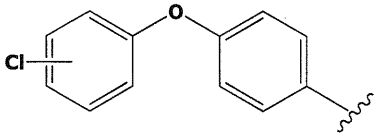




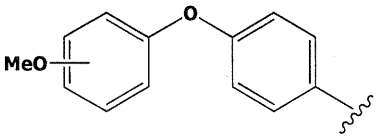
~~xxiii~~ ~~xxiv~~ ~~xxv~~

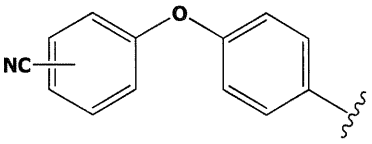




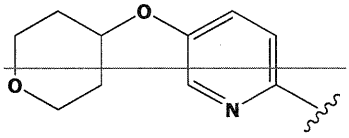


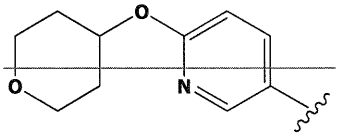
~~xxvi~~ *xxvii* *xxviii*

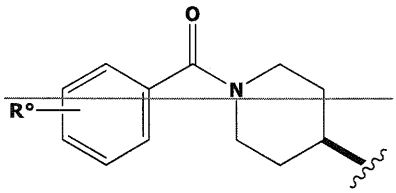




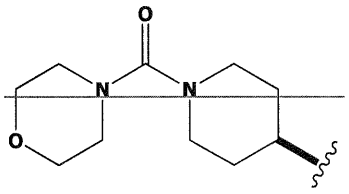
xxix *xxx*

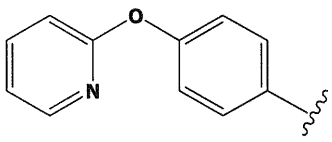


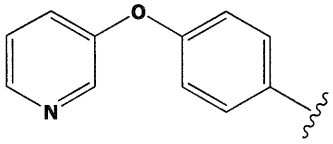




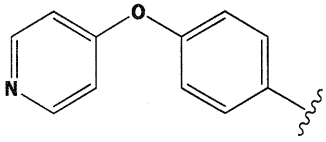
~~xxxi~~ ~~xxxii~~ ~~xxxiii~~

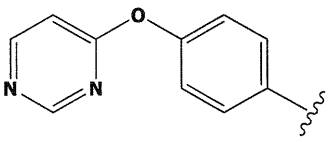


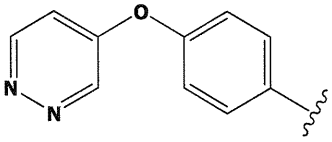




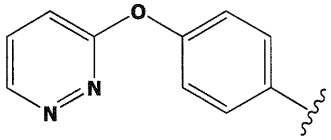
~~xxxiv~~ *xxxv* *xxxvi*

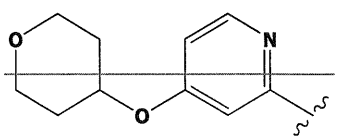


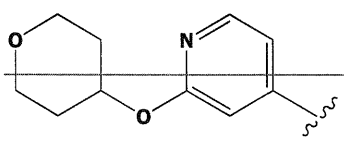




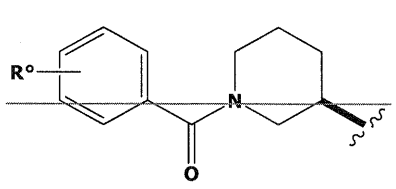
xxxvii *xxxviii* *xxxix*



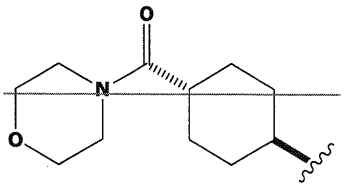




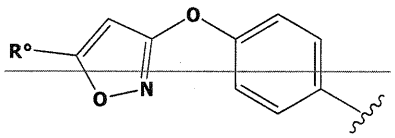
xl ~~xli~~ ~~xliii~~



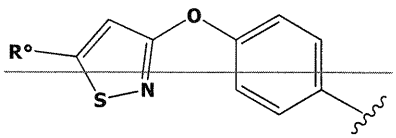
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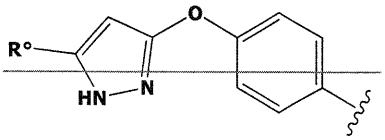
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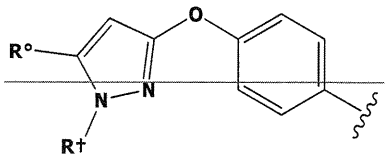
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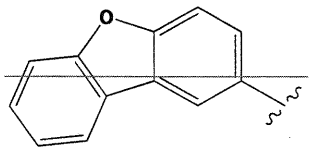
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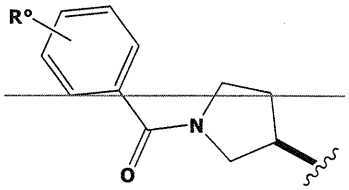
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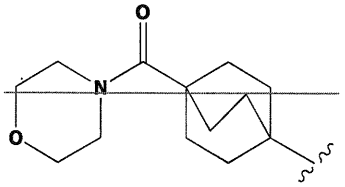
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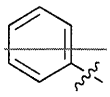
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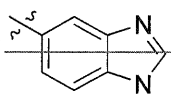
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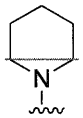
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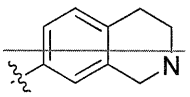
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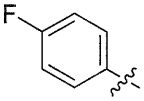
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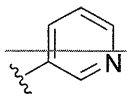
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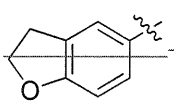
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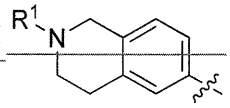
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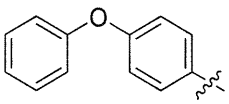
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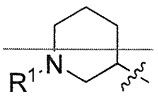
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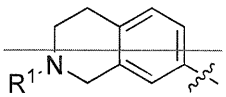
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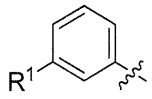
lx



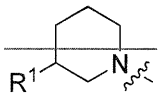
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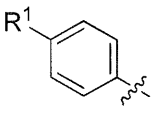
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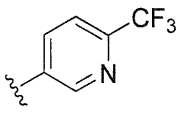
lxiii



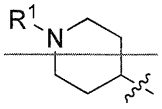
lxv



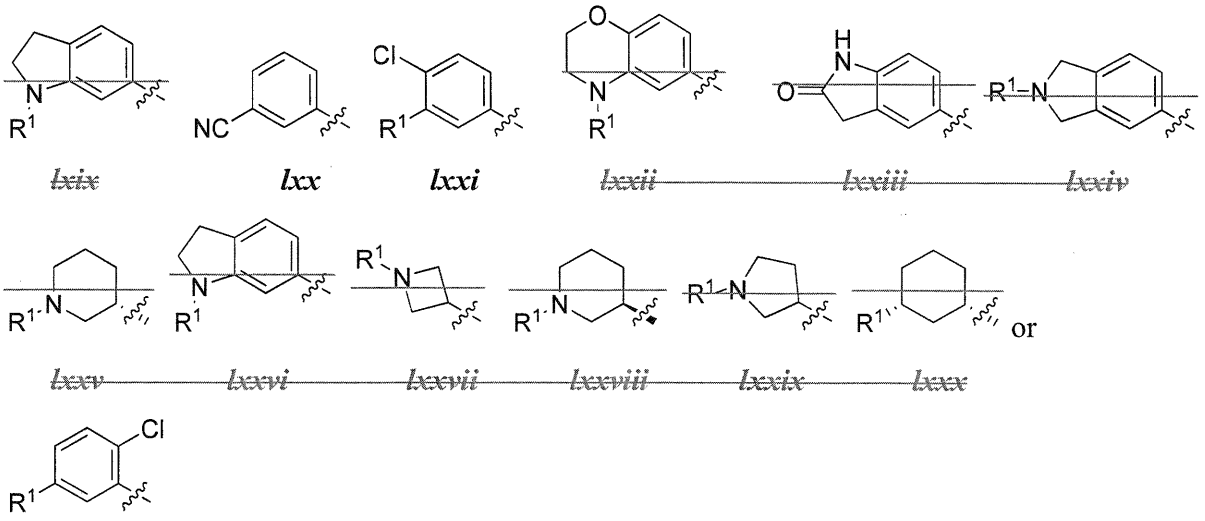
lxvi



lxvii



lxviii



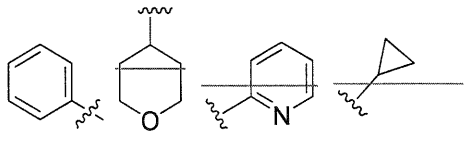
~~*lxix*~~ ***lxx*** ***lxxi*** ~~*lxxii*~~ ~~*lxxiii*~~ ~~*lxxiv*~~

~~*lxxv*~~ ~~*lxxvi*~~ ~~*lxxvii*~~ ~~*lxxviii*~~ ~~*lxxix*~~ ~~*lxxx*~~

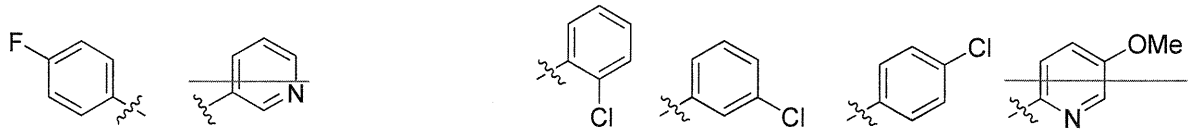
lxxxi.

~~34~~. The compound according to claim ~~23~~, wherein Ring A is selected from ***i***, ***ii***, ***v***, ***vi***, ***vii***, ***ix***, ***xiv***, ***xvi***, ~~*iii*~~, ***lxiii***, ***lxxi***, ~~*lxxiv*~~, ~~*lxxvi*~~, ~~*lxxviii*~~, and ***lxxxi***.

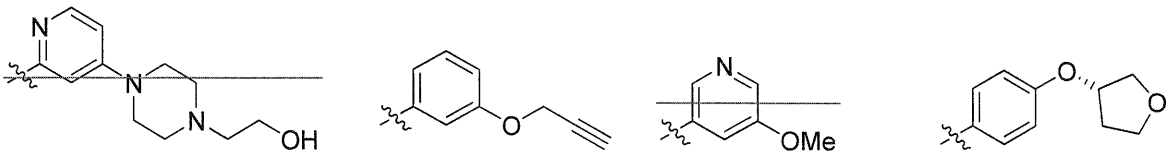
~~45~~. The compound according to claim 1 or claim 2, wherein Ring B is selected from:



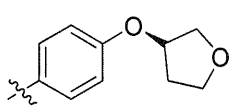
xi ~~*xii*~~ ~~*xiii*~~ ~~*xiv*~~



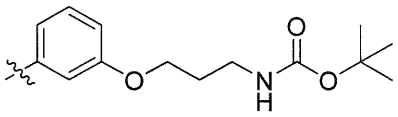
xv ~~*xvi*~~ ***xviii*** ***xix*** ***xx*** ~~*xxi*~~



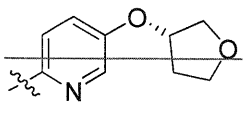
~~*xxii*~~ ***xxiii*** ~~*xxiv*~~ ***xxv***



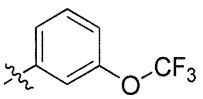
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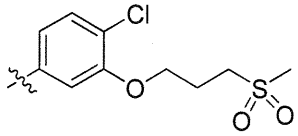
xxvii



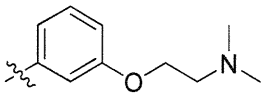
~~*xxviii*~~



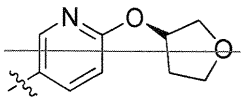
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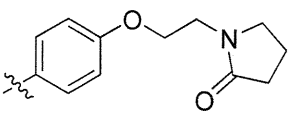
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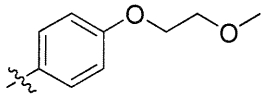
xxxi



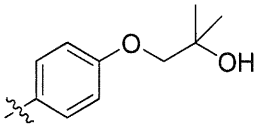
~~*xxxii*~~



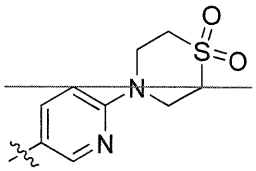
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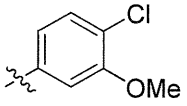
xxxiv



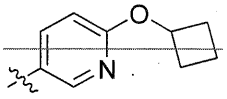
xxxv



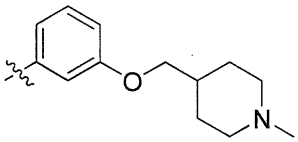
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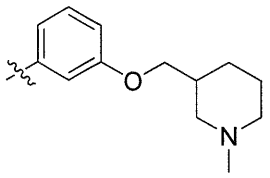
xxxvii



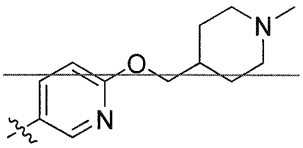
~~*xxxviii*~~



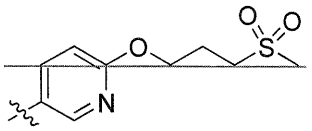
xxxix



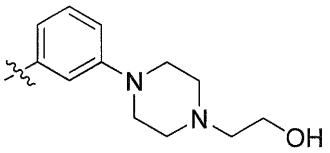
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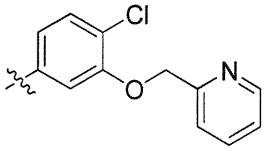
~~*xlii*~~



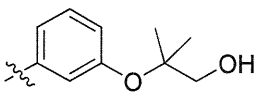
~~*xliii*~~



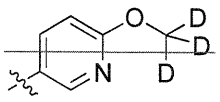
xliv



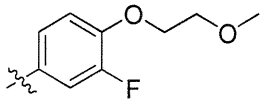
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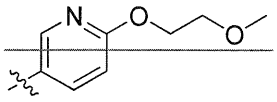
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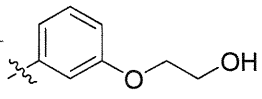
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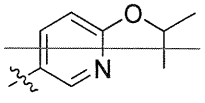
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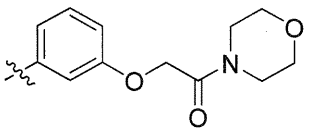
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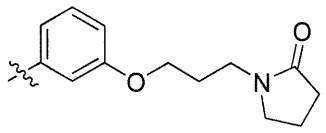
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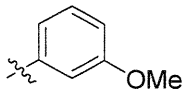
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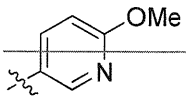
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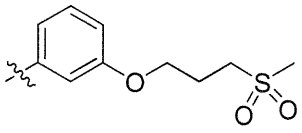
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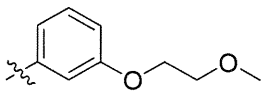
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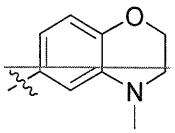
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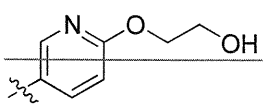
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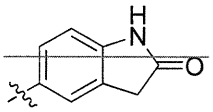
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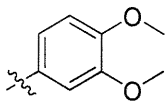
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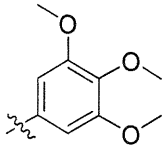
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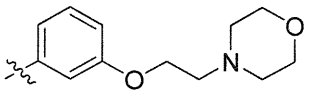
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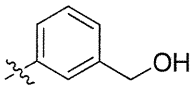
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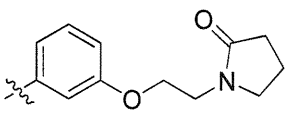
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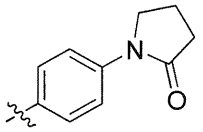
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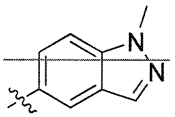
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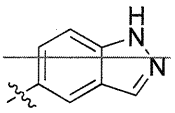
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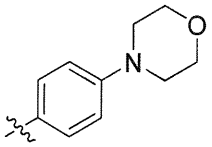
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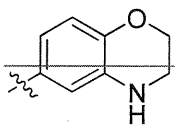
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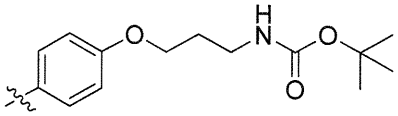
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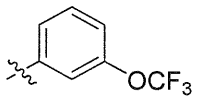
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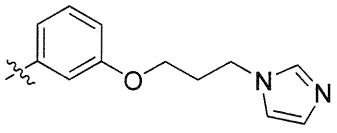
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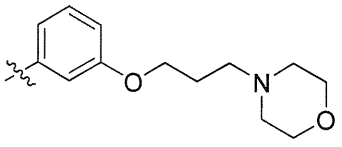
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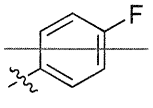
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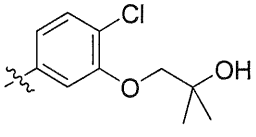
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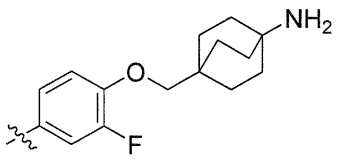
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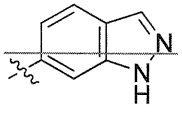
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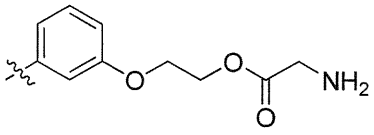
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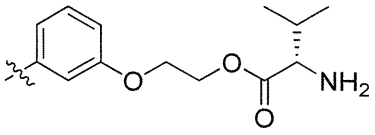
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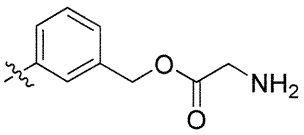
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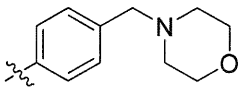
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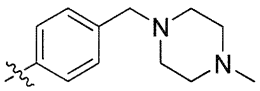
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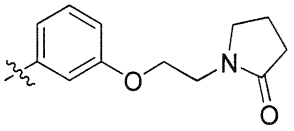
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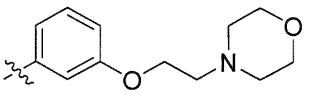
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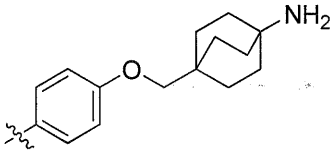
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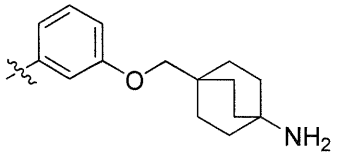
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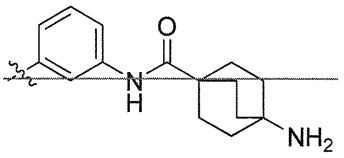
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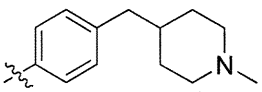
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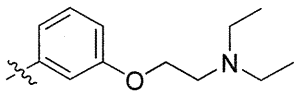
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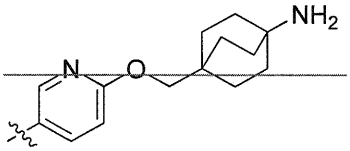
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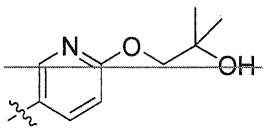
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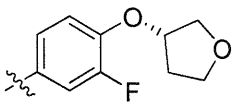
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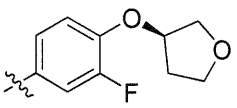
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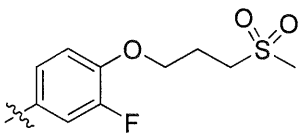
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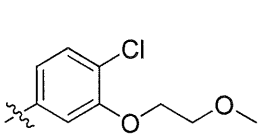
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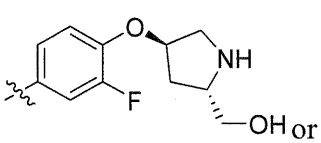
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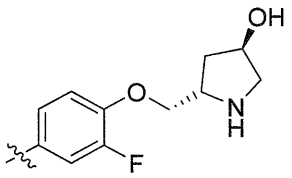
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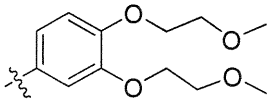
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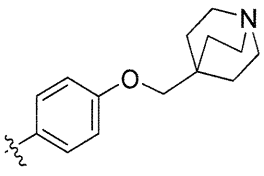
cvi or



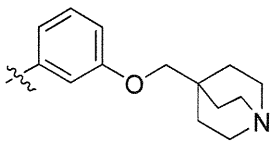
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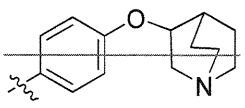
cviii



cix



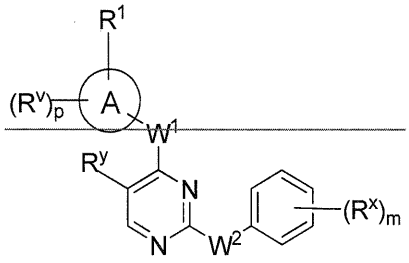
cx



~~*cxi.*~~

~~56~~. The compound according to claim ~~45~~, wherein Ring B is selected from ***xi***, ~~***xiii***, ***xvi***,~~ ***xvii***, ***xix***, ***xx***, ***xxv***, ***xxvi***, ~~***xxxii***,~~ ***xxxiv***, ***xxxv***, ~~***xxxviii***, ***xlii***,~~ ***xlvi***, ***xlviii***, ***l***, ***lviii***, ***lxiv***, ***lxxviii***, ***lxxxiii***, ***xciv***, ~~***c***, ***ci***,~~ ***cii***, ***ciii***, ***civ***, and ***cv***.

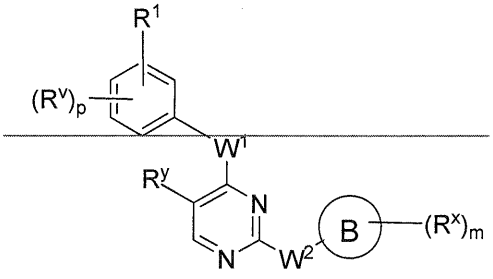
~~6. The compound according to claim 1, wherein said compound is of formula II-b:~~



~~II-b~~

~~or a pharmaceutically acceptable salt thereof.~~

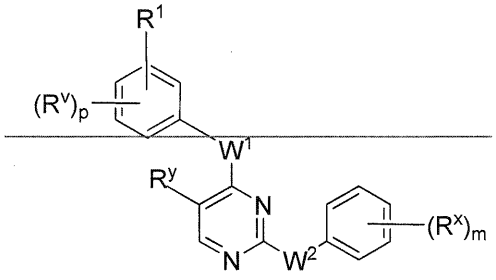
~~7. The compound according to claim 1, wherein said compound is of formula III-b:~~



~~III-b~~

~~or a pharmaceutically acceptable salt thereof.~~

~~8. The compound according to claim 6 or claim 7, wherein said compound is of formula IV-b:~~



~~IV-b~~

~~or a pharmaceutically acceptable salt thereof.~~

~~9~~7. 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 ~~additional~~ 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 Y is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

~~10~~8. 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 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 ~~or two~~ additional methylene units of L ~~are~~ is optionally ~~and independently~~ replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and

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

~~11~~9. The compound according to claim ~~1~~8, 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 ~~or two~~ additional methylene ~~units~~ unit of L ~~are~~ is optionally ~~and independently~~ replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

~~12~~10. The compound according to claim ~~1~~8, 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)-.

~~13~~11. The compound according to claim ~~12~~8, wherein L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH$_2$N(CH$_3$)-, -NRC(O)CH=CHCH$_2$O-, -CH$_2$NRC(O)CH=CH-, -NRSO$_2$CH=CH-, -NRSO$_2$CH=CHCH$_2$-, ~~-NRC(O)(C=N$_2$)-, -NRC(O)(C=N$_2$)C(O)-,~~ or -NRC(O)C(=CH$_2$)CH$_2$~~-, -CH$_2$NRC(O)-, -CH$_2$CH$_2$NRC(O)-, or -CH$_2$NRC(O)cyclopropylene-~~; wherein R is H or optionally substituted C_{1-6} aliphatic; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

~~14~~12. The compound according to claim ~~15~~11, wherein L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH$_2$N(CH$_3$)-, -NHC(O)CH=CHCH$_2$O-, -CH$_2$NHC(O)CH=CH-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH$_2$-, ~~-NHC(O)(C=N$_2$)-, -NHC(O)(C=N$_2$)C(O)-,~~ or -NHC(O)C(=CH$_2$)CH$_2$~~-, -CH$_2$NHC(O)-, -CH$_2$CH$_2$NHC(O)-, or -CH$_2$NHC(O)cyclopropylene-~~.

13. The compound according to claim 2, wherein L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH$_2$N(CH$_3$)-, -NRC(O)CH=CHCH$_2$O-, -CH$_2$NRC(O)CH=CH-, -NRSO$_2$CH=CH-, -NRSO$_2$CH=CHCH$_2$-, -NRC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NRC(O)-, -CH$_2$CH$_2$NRC(O)-, or -CH$_2$NRC(O)cyclopropylene-; wherein R is H or optionally substituted C_{1-6} aliphatic; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

14. The compound according to claim 13, wherein L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH$_2$N(CH$_3$)-, -NHC(O)CH=CHCH$_2$O-, -CH$_2$NHC(O)CH=CH-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH$_2$-, -NHC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NHC(O)-, -CH$_2$CH$_2$NHC(O)-, or -CH$_2$NHC(O)cyclopropylene-.

15. 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$_2$N(R)-, -S-, -S(O)-, -SO$_2$-, -OC(O)-, or –C(O)O-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

~~16. 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 or two additional methylene units of L are independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO$_2$-, -SO$_2$N(R)-, -S-, -S(O)-, -SO$_2$-, -OC(O)-, or -C(O)O-;~~

17. The compound according to claim 1, wherein:

L is a covalent bond, -C(O)-, -N(R)C(O)-, -NH-, $-CH_2NH-$, $-NHCH_2-NHC(O)CH_2OC(O)-$, $-CH_2NHC(O)-$, $-NHSO_2-$, $-NHSO_2CH_2-$, $-NHC(O)CH_2OC(O)-$, or $-SO_2NH-$, or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and

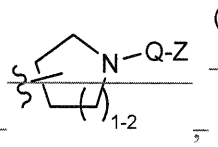
Y is selected from the following (*i*), (*ii*), (*iv*), (*v*), (*vi*), (*vii*), (*viii*), (*ix*), (*x*), (*xi*), (*xii*), (*xiii*), (*xiv*) or (*xvii*):

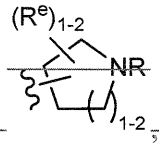
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN;

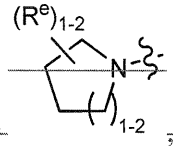
(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) 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

(*iv*) 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

(*v*) 

, 

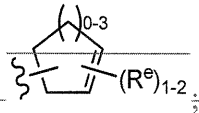
, or 

, wherein each R, Q, Z; or

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

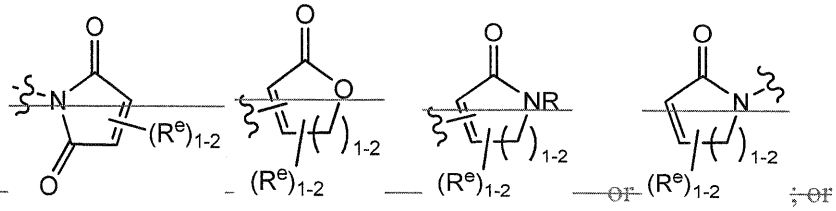
(*vii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

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

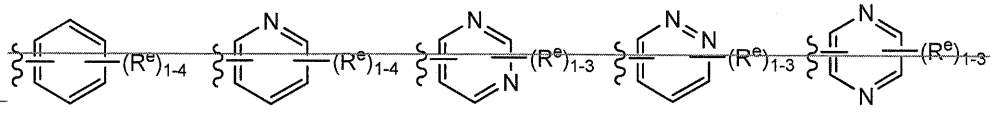
(*ix*) 

; or

(*x*) 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

(*xi*)  ; or

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

(*xiii*) 

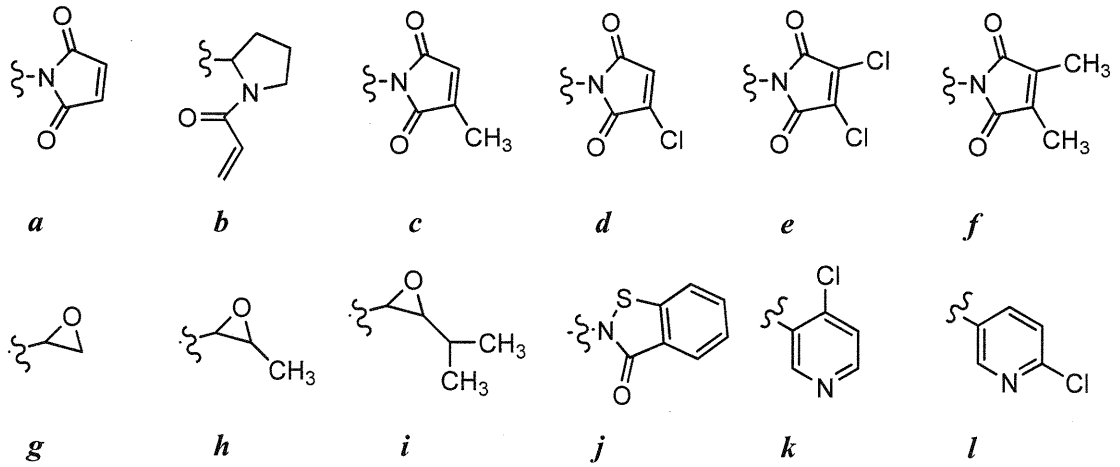
wherein each R^e is as defined above and described herein; or

(*xiv*) 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.

1816. The compound according to claim 171, wherein L is a covalent bond, $-CH_2-$, -NH-, -C(O)-, $-CH_2NH-$, $-NHCH_2-$, –NHC(O)-, $-NHC(O)CH_2OC(O)-$, $-CH_2NHC(O)-$, $-NHSO_2-$, $-NHSO_2CH_2-$, ~~-NHC(O)CH$_2$OC(O)-,~~ or $-SO_2NH-$.

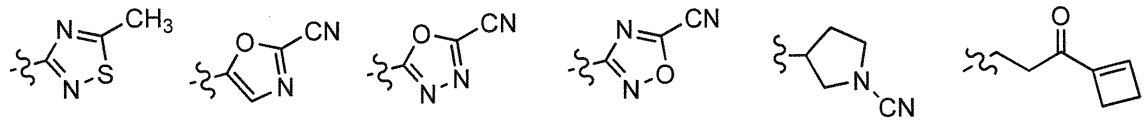
1917. The compound according to claim 1816, wherein L is a covalent bond.

2018. The compound according to claim 16 or 17, wherein Y is selected from:

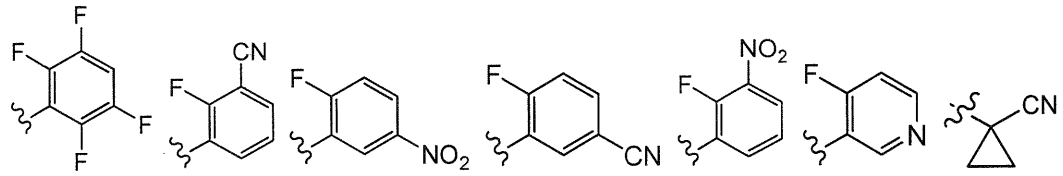


a ***b*** ***c*** ***d*** ***e*** ***f***

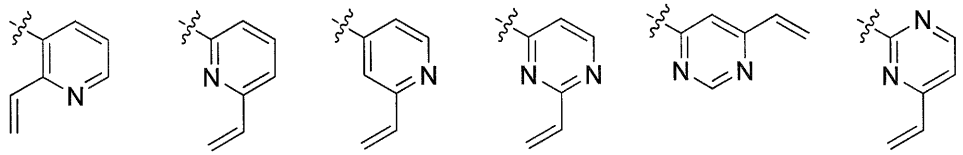
g ***h*** ***i*** ***j*** ***k*** ***l***



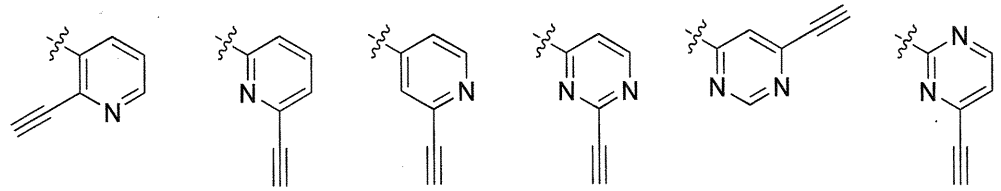
m *n* *o* *p* *q* *r*



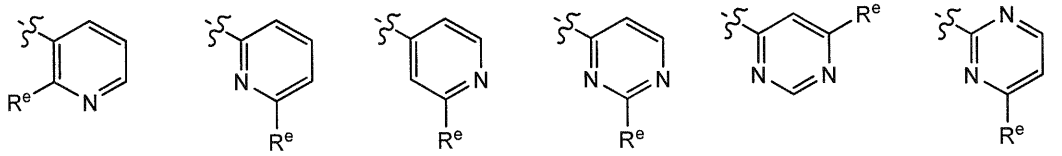
s *t* *u* *v* *w* *x* *y*



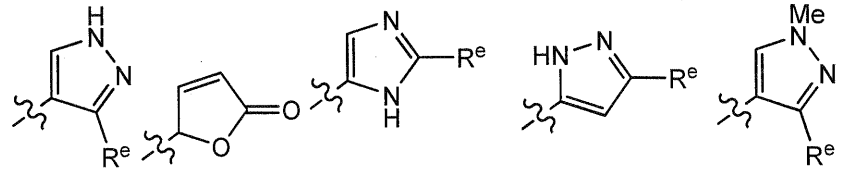
z *aa* *bb* *cc* *dd* *ee*



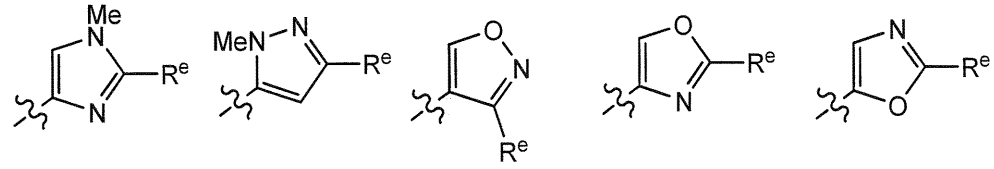
ff *gg* *hh* *ii* *jj* *kk*



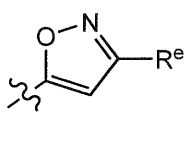
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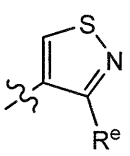
rr *ss* *tt* *uu* *vv*



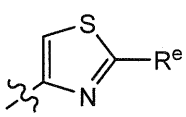
ww *xx* *yy* *zz* *aaa*



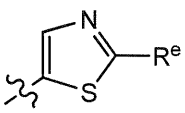
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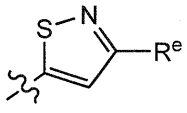
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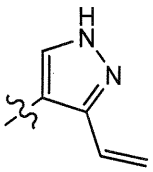
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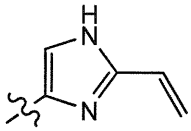
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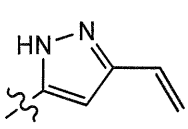
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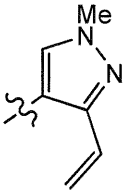
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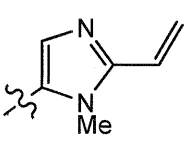
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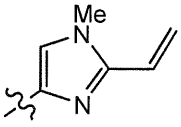
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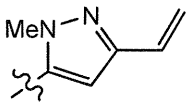
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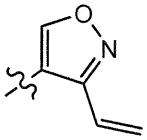
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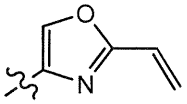
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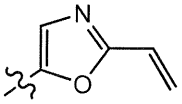
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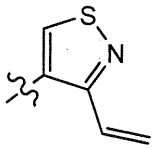
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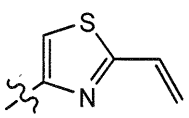
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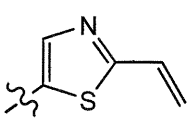
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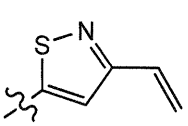
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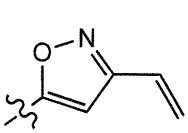
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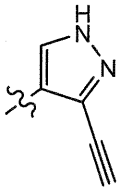
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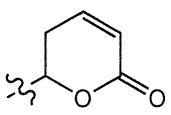
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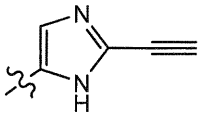
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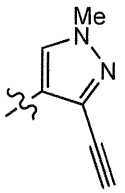
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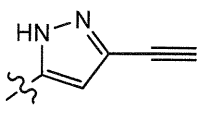
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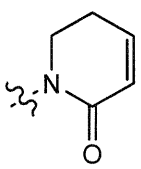
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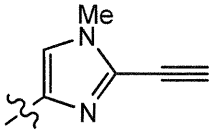
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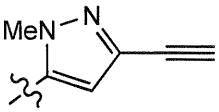
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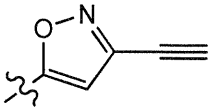
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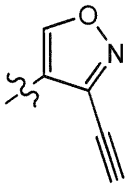
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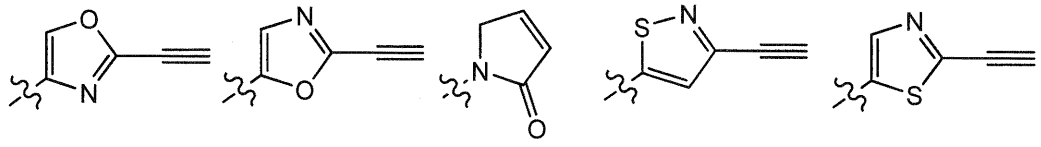
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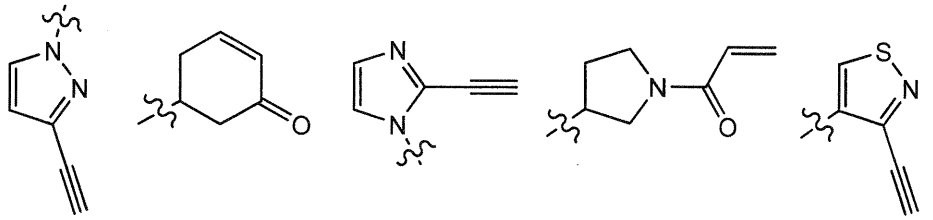
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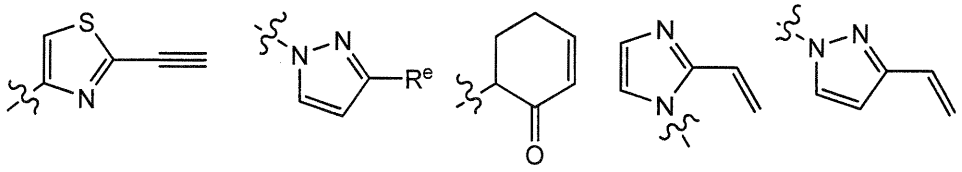
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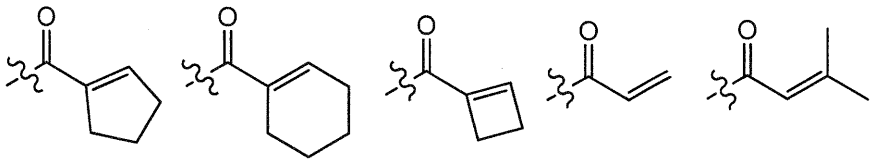
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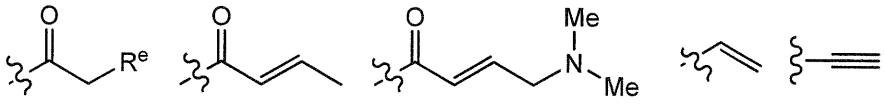
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oooo *pppp* *qqqq* *rrrr* *ssss*



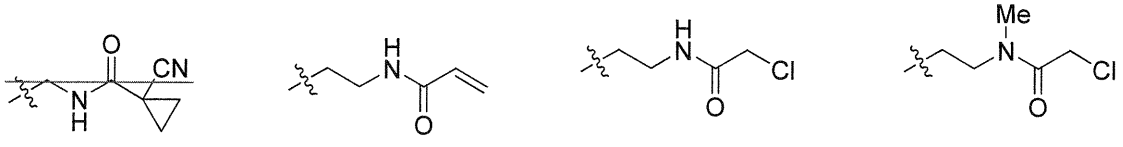
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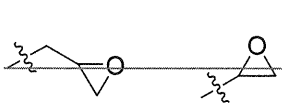
yyyy *zzzz* *aaaaa* *bbbbb* *ccccc*

wherein each R^e is independently selected from halogen.

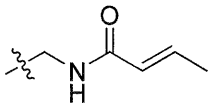
~~21~~19. The compound according to claim 1, wherein R^1 is selected from:



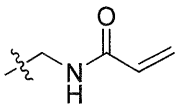
a *b* *c* *d*



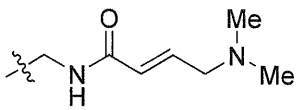
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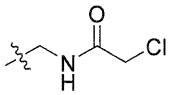
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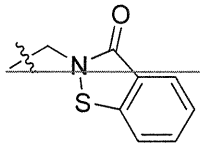
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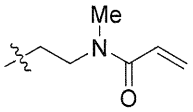
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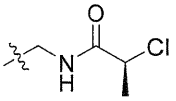
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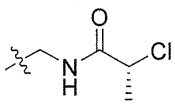
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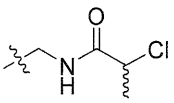
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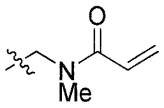
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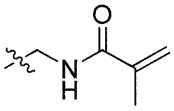
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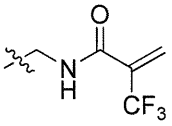
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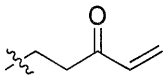
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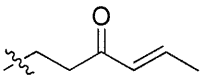
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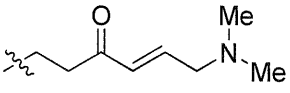
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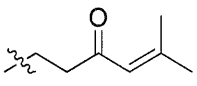
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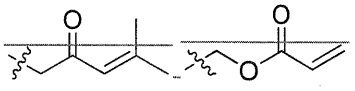
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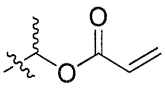
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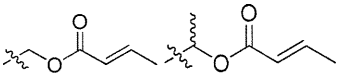
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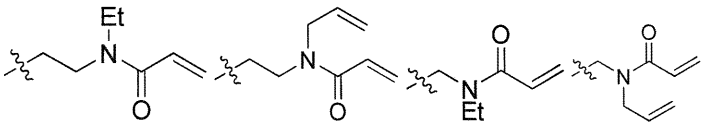
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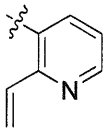
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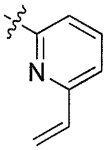
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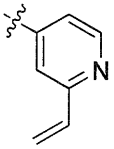
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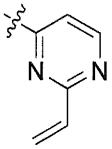
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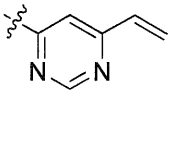
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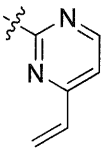
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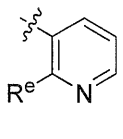
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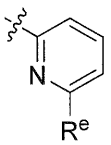
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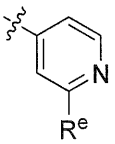
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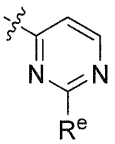
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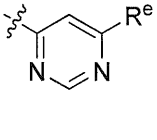
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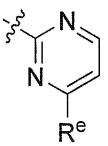
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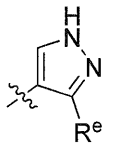
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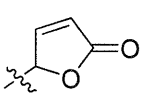
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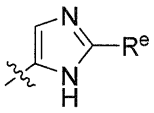
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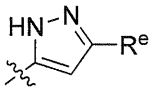
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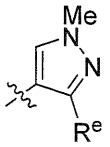
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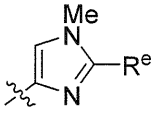
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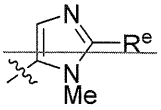
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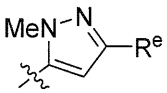
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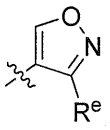
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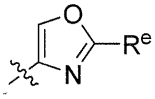
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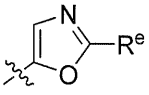
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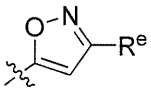
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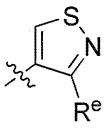
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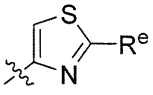
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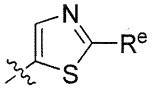
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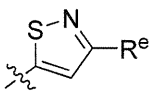
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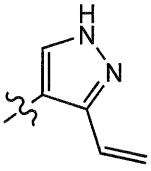
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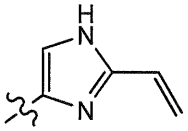
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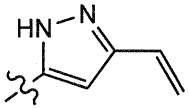
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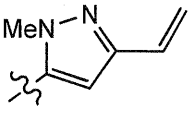
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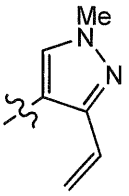
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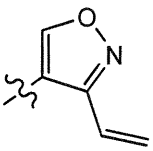
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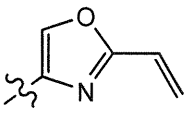
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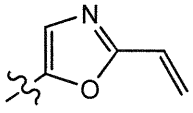
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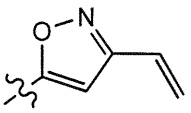
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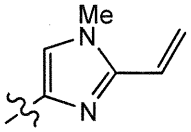
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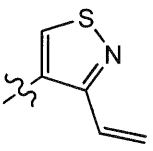
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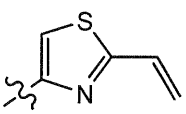
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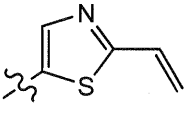
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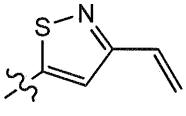
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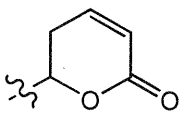
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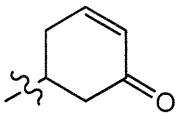


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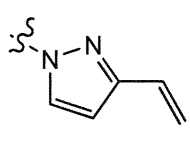


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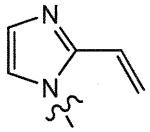




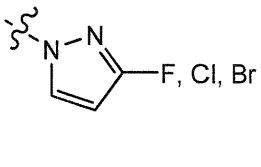
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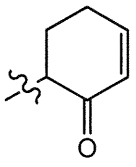


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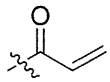


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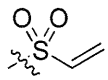




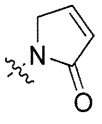
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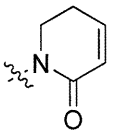
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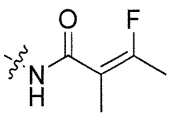
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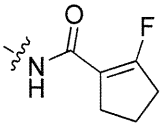
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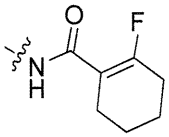
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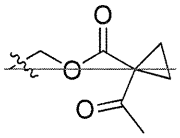
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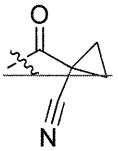
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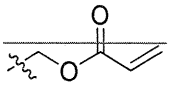
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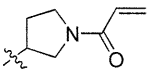
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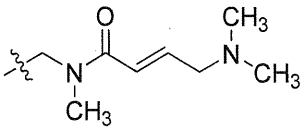
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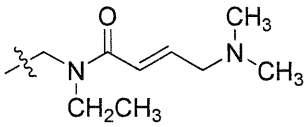
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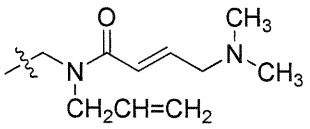
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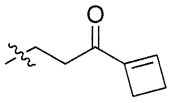
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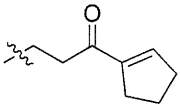
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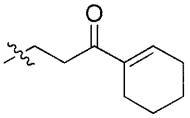
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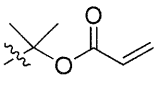
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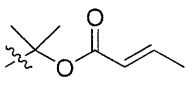
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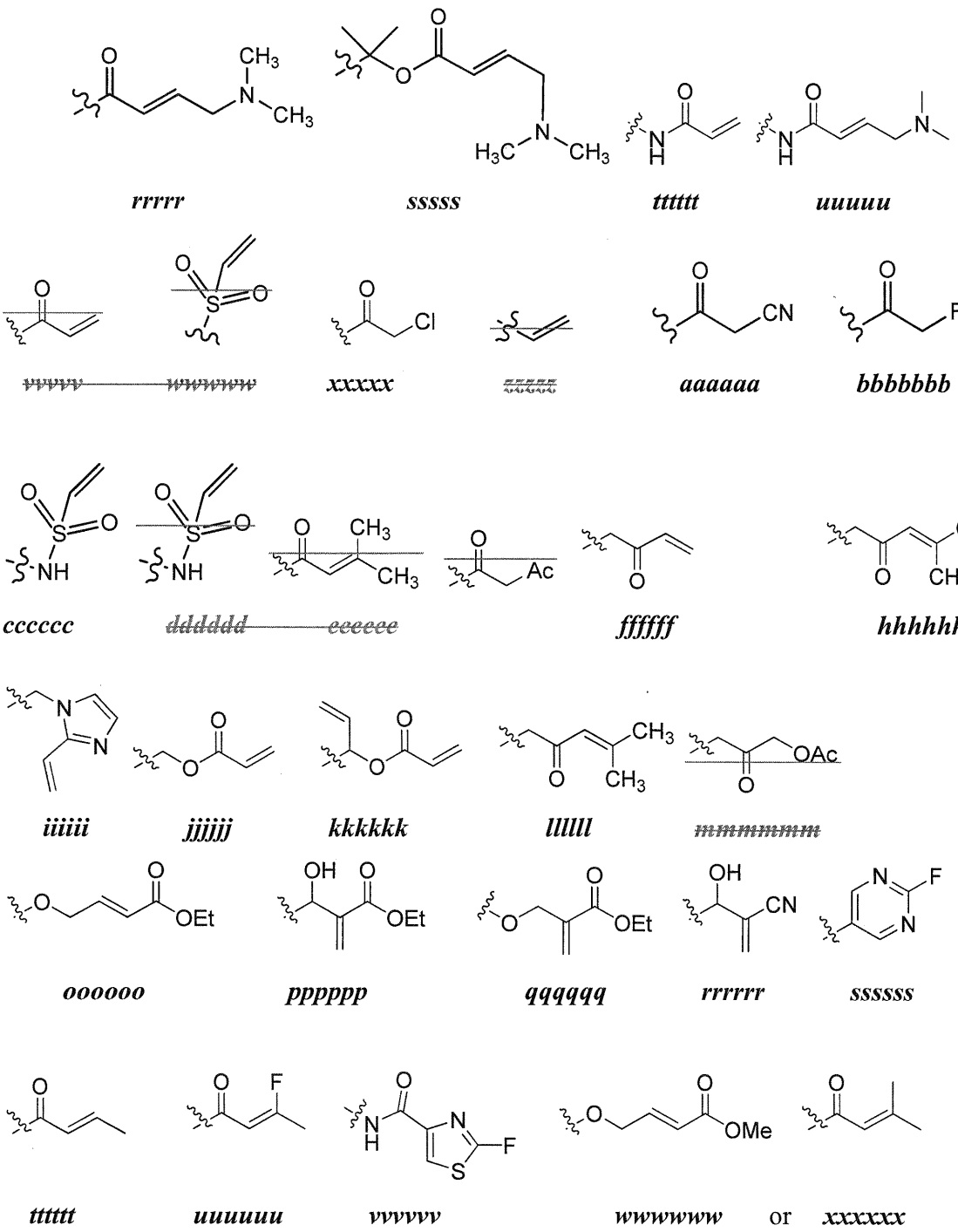
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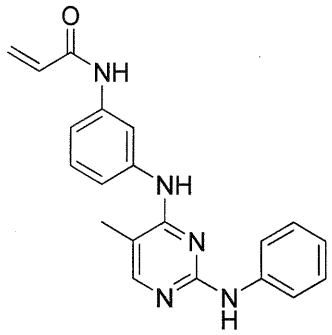


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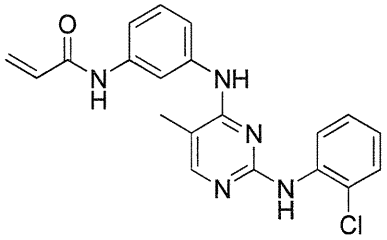


wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

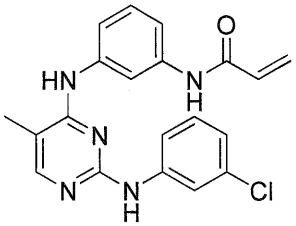
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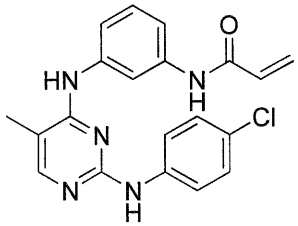
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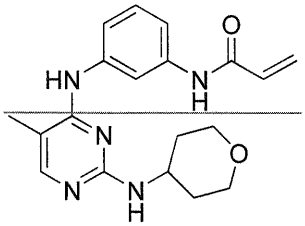
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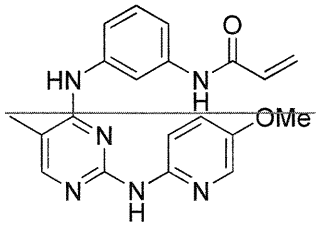
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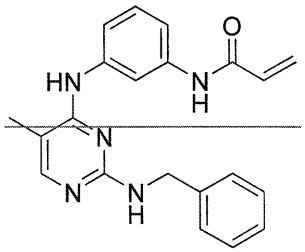
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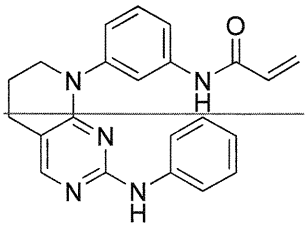
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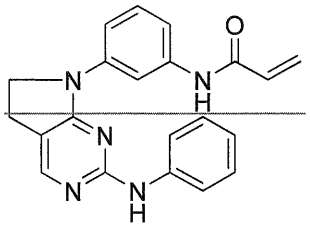
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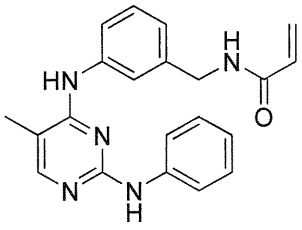
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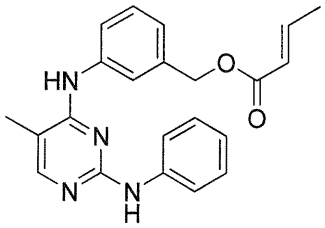
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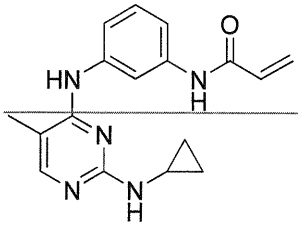
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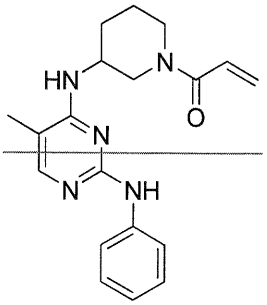
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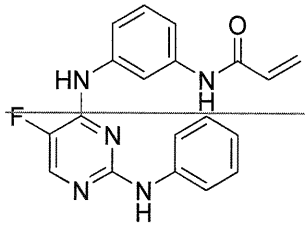
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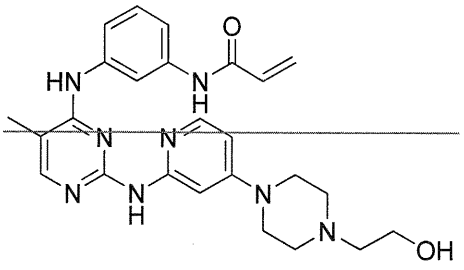
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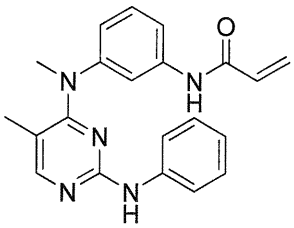
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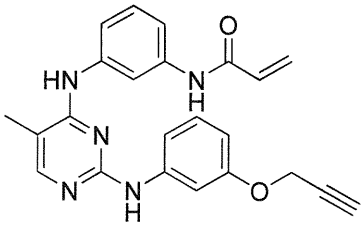
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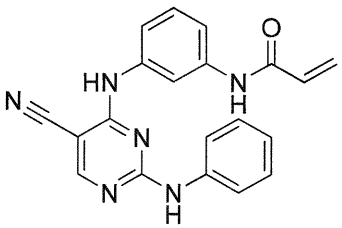
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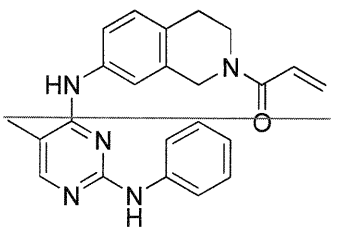
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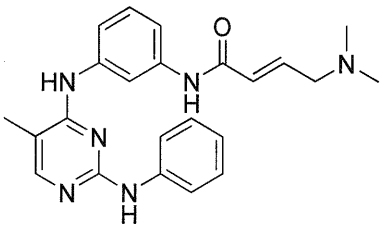
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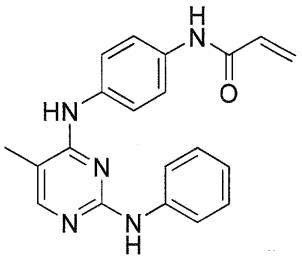
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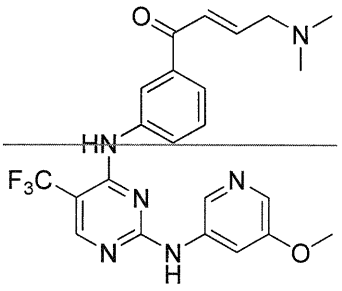
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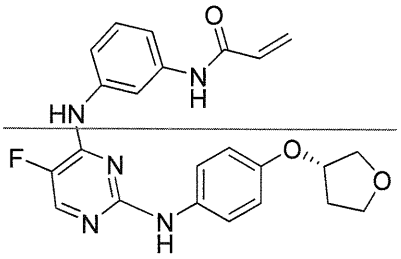
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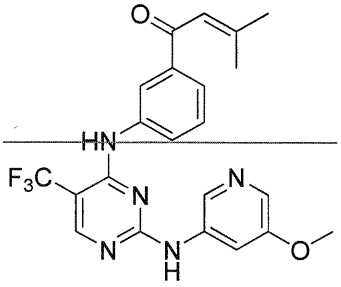
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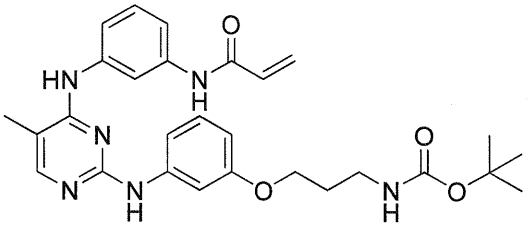
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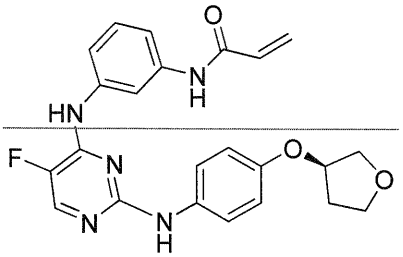
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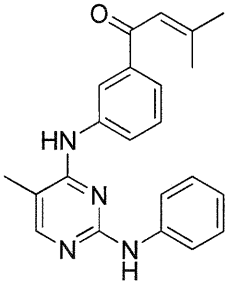
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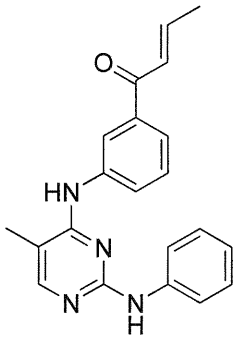
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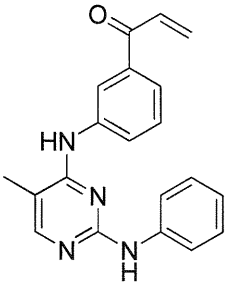
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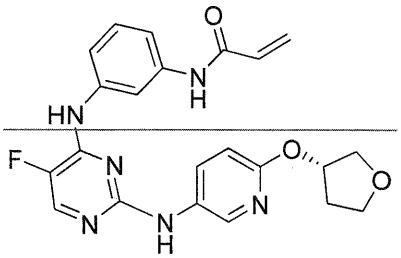
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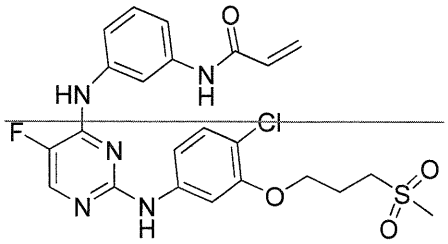
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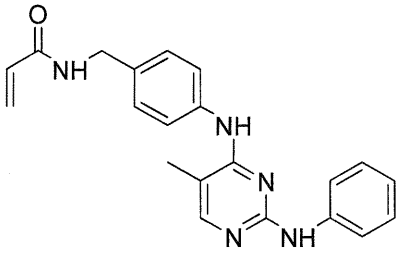
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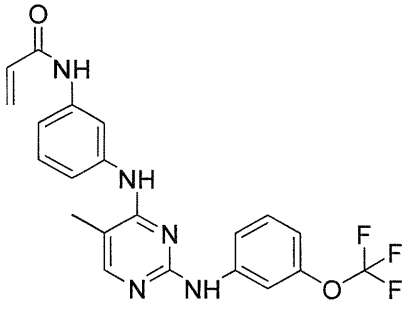
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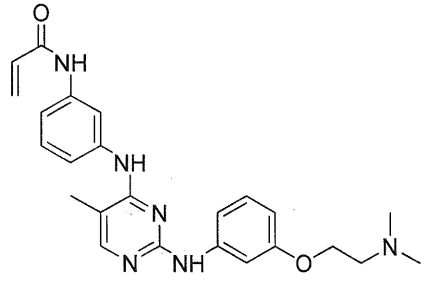
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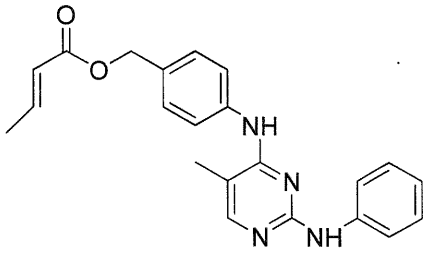
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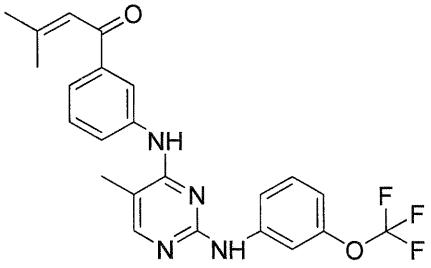
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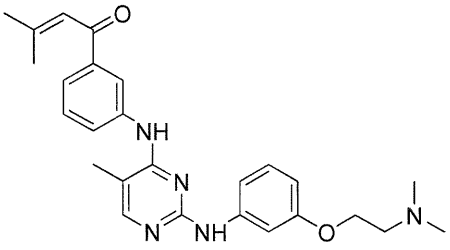
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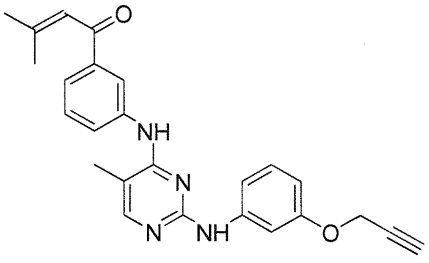
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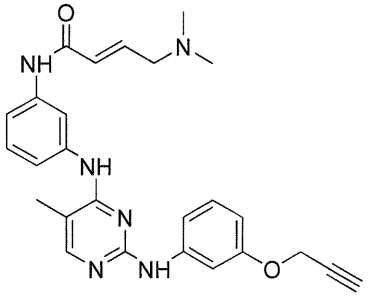
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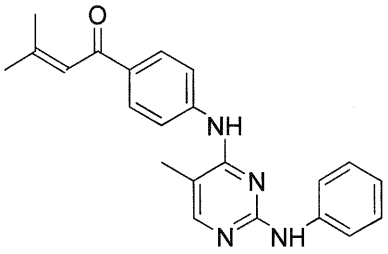
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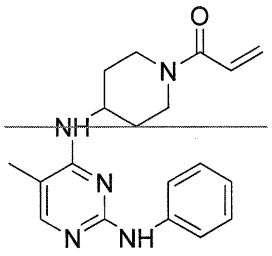
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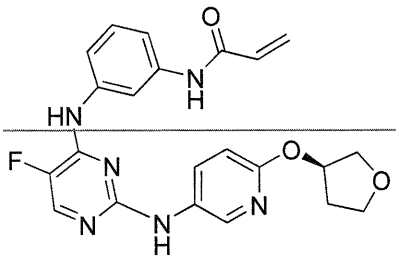
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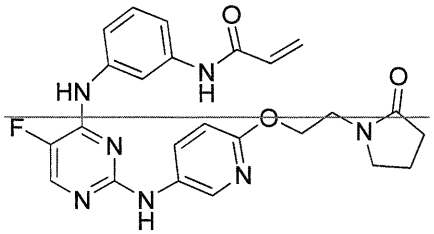
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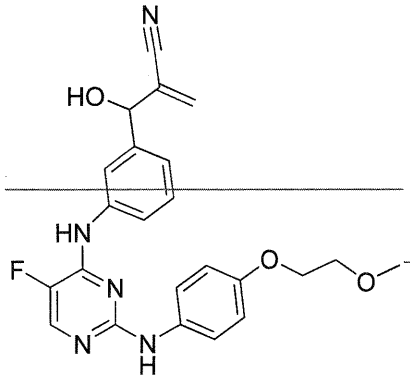
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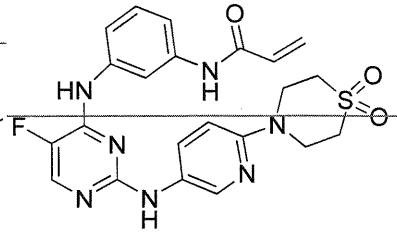
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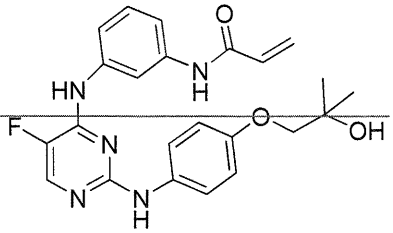
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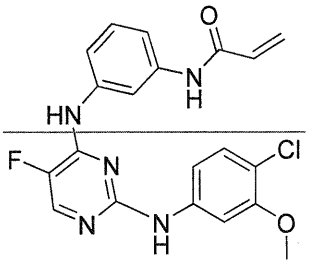
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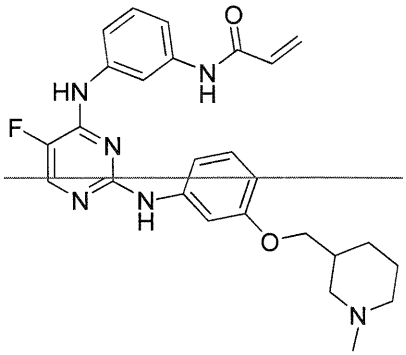
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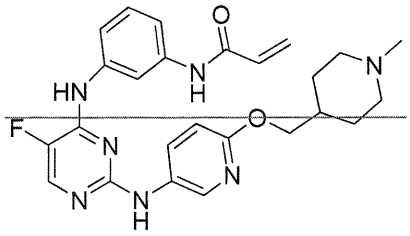
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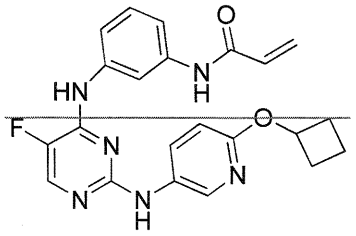
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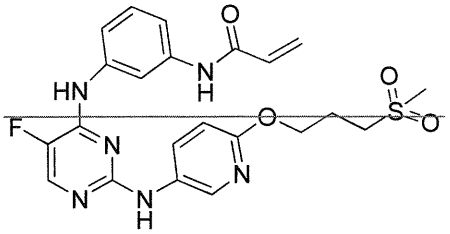
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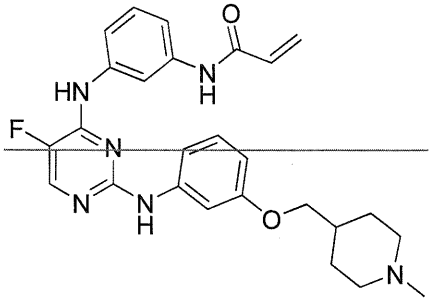
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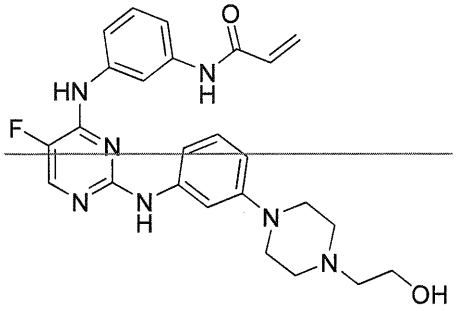
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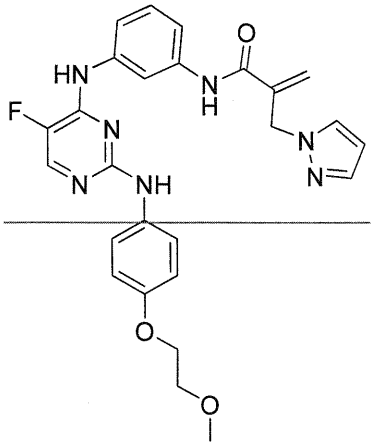
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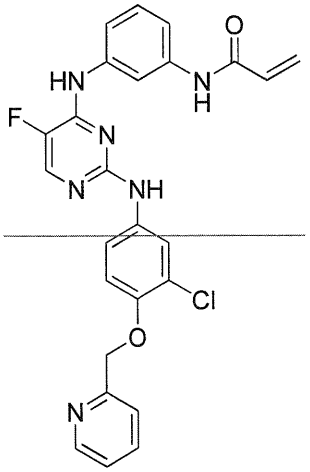
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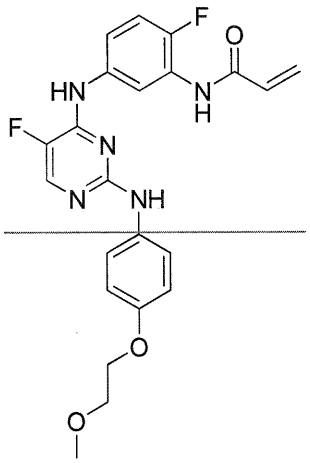
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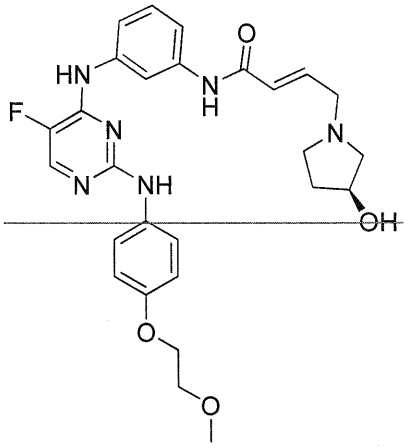
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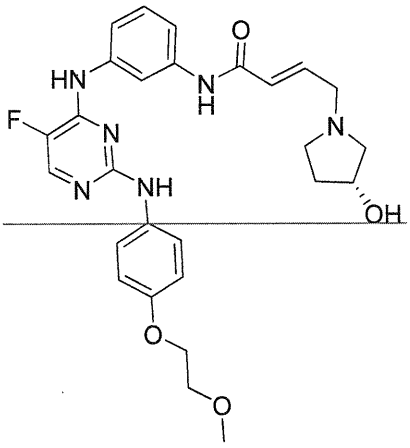
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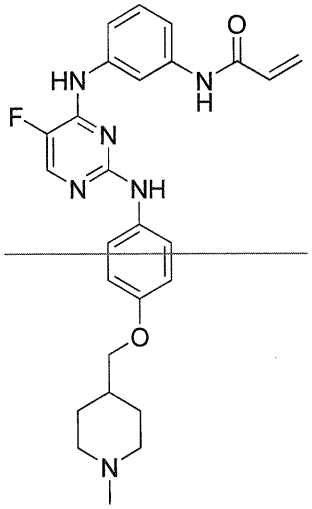
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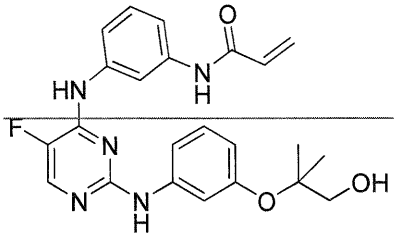
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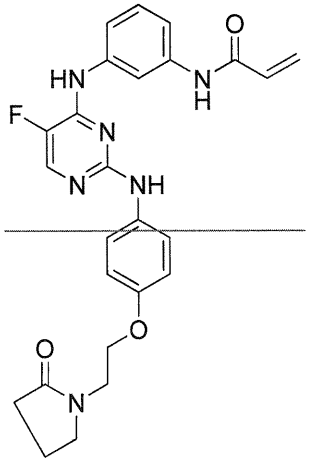
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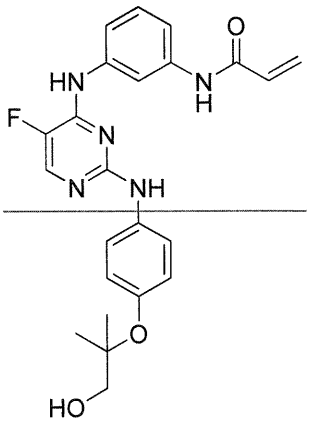
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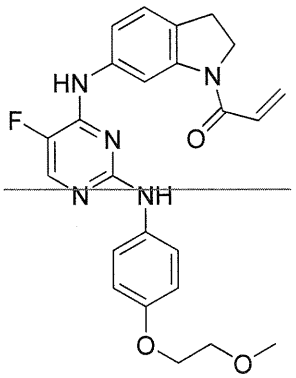
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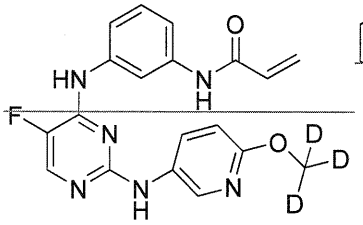
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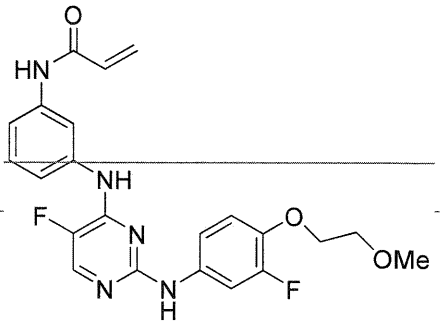
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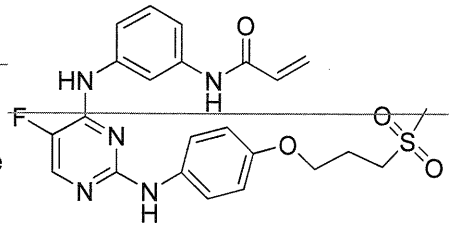
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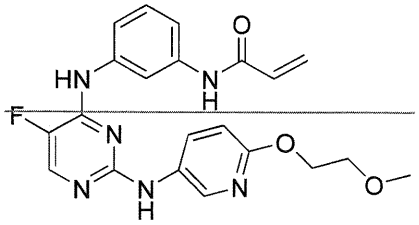
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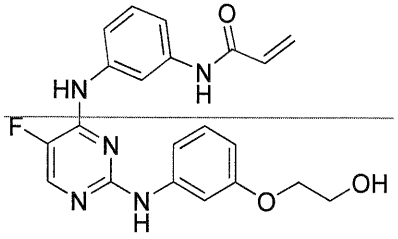
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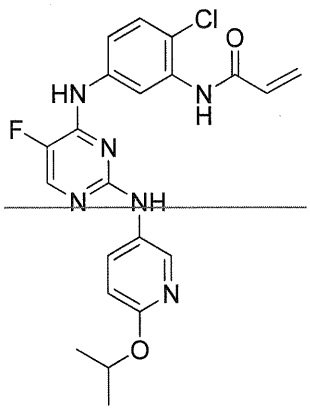
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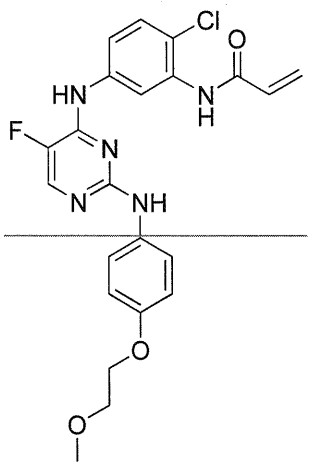
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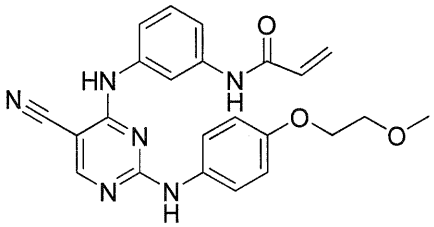
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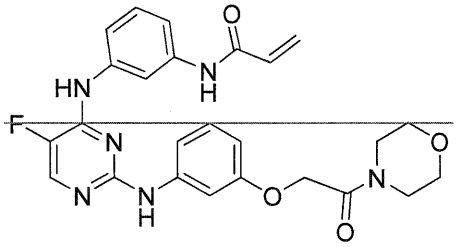
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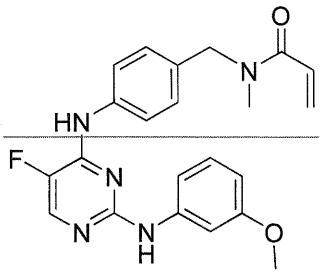
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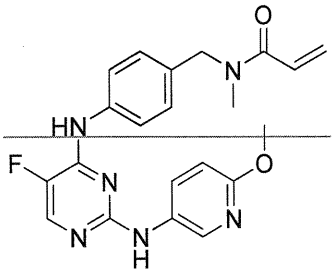
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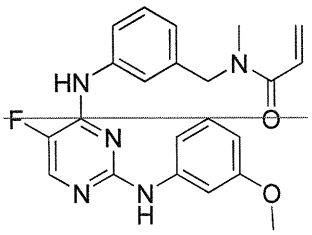
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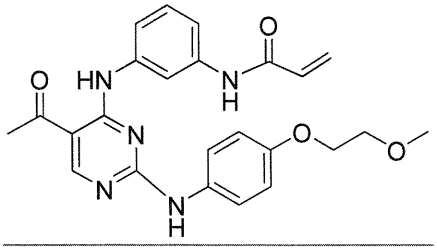
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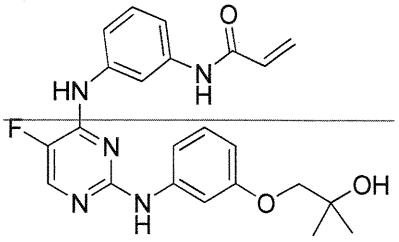
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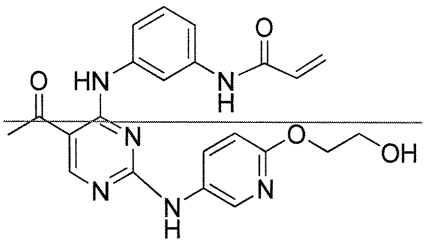
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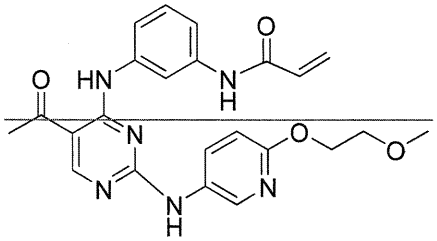
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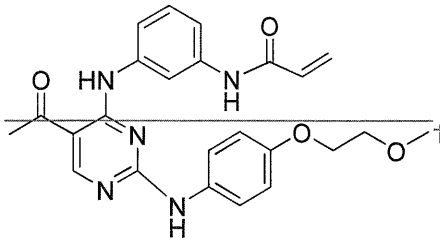
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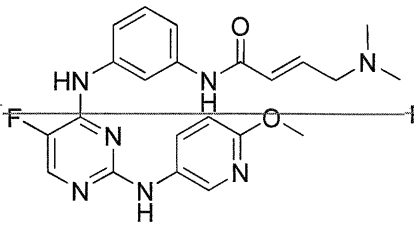
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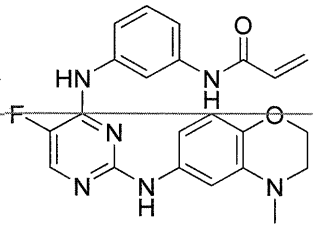
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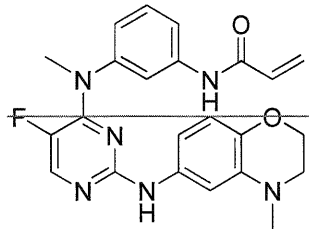
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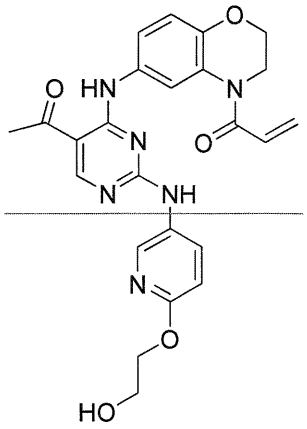
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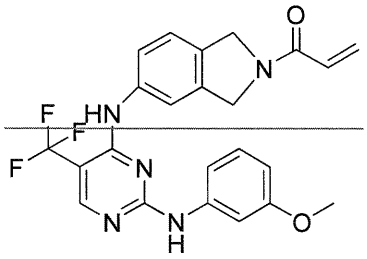
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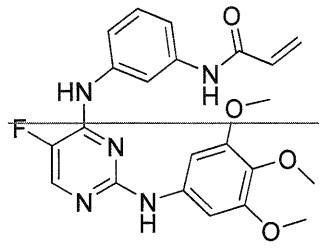
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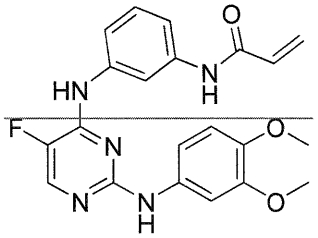
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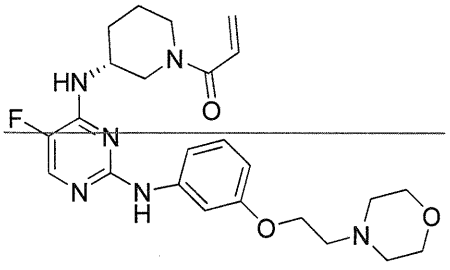
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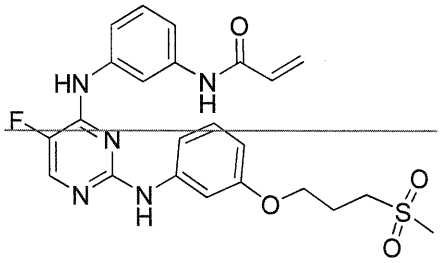
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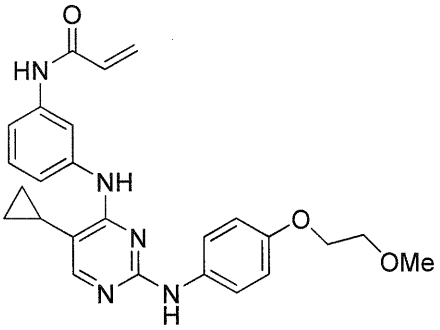
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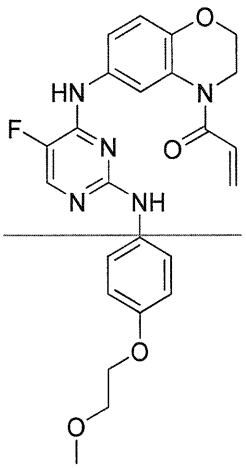
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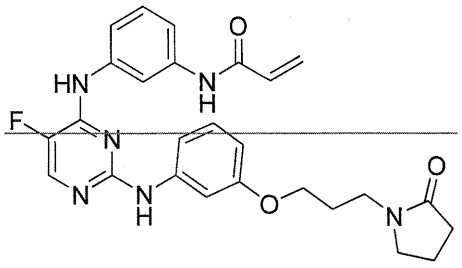
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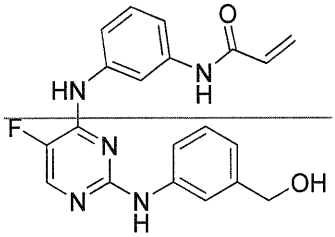
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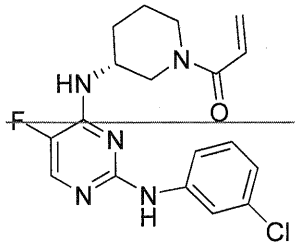
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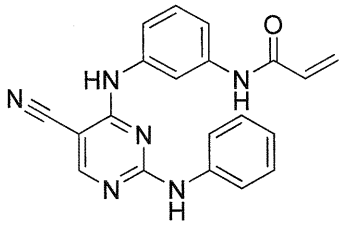
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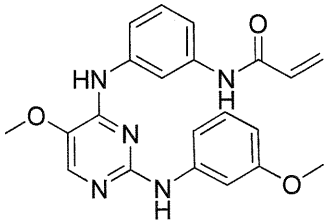
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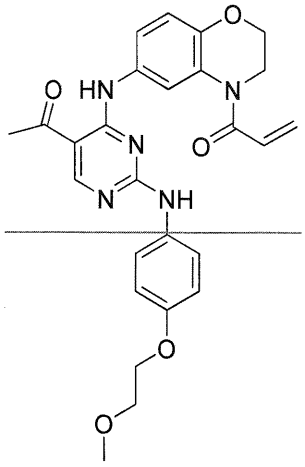
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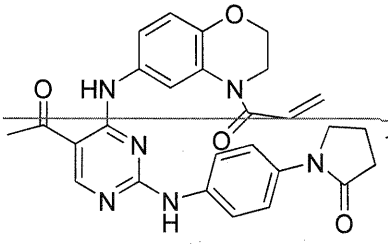
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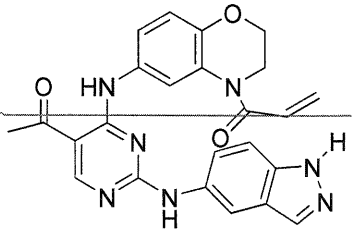
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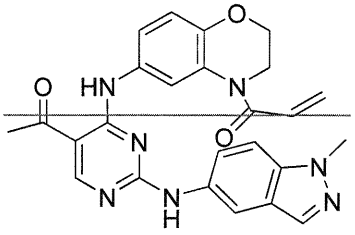
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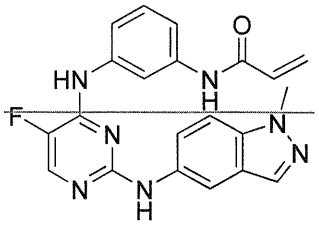
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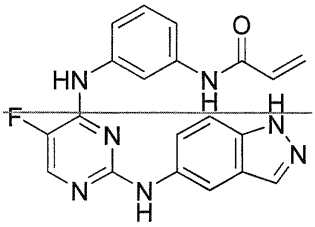
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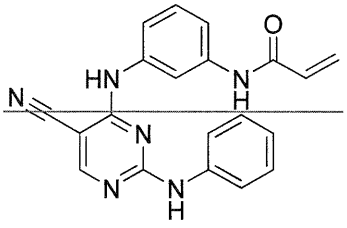
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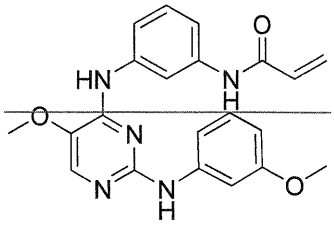
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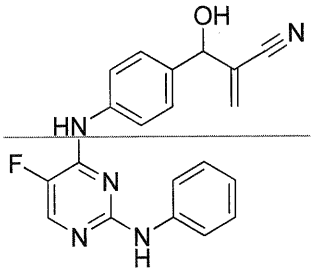
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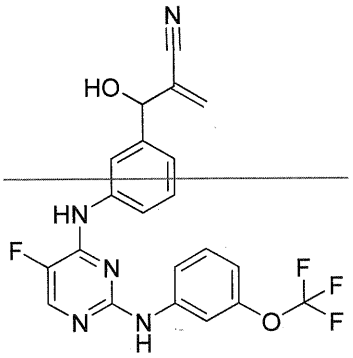
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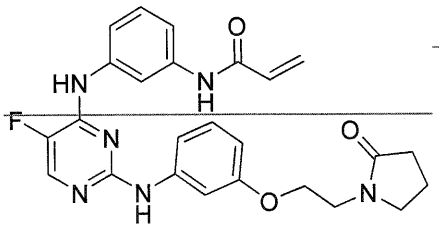
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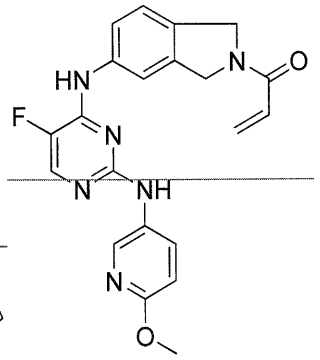
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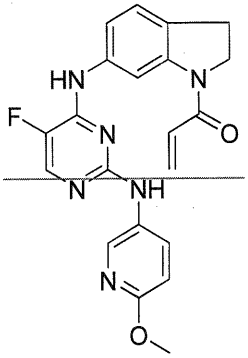
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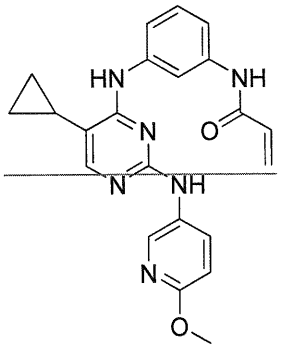
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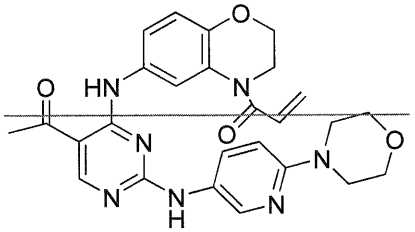
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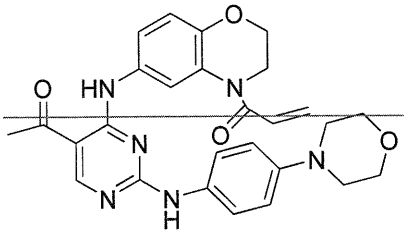
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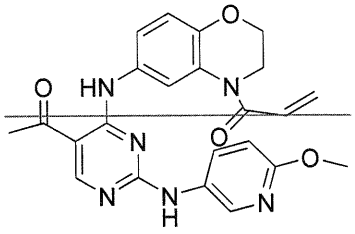
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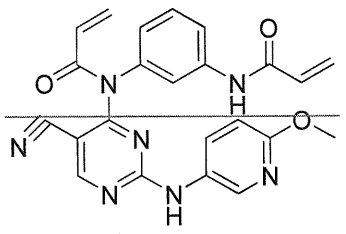
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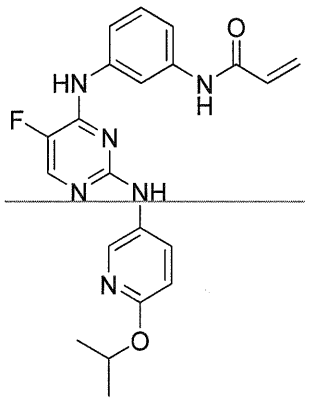
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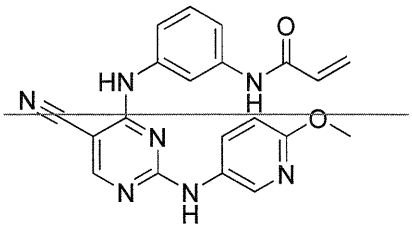
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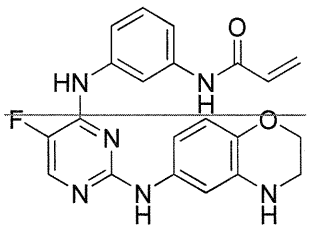
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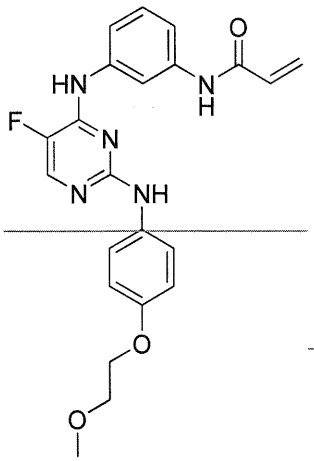
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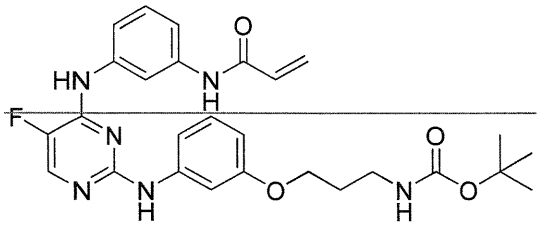
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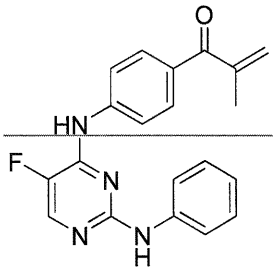
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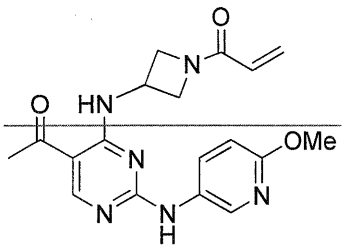
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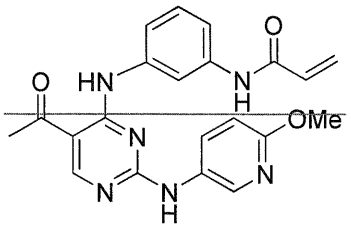
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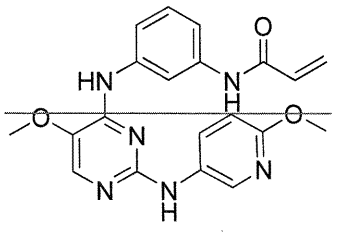
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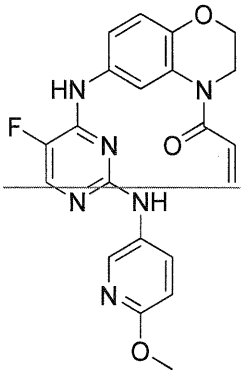
I-187



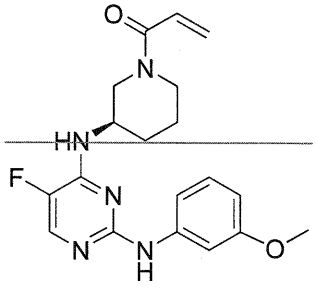
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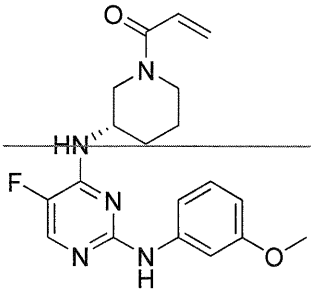
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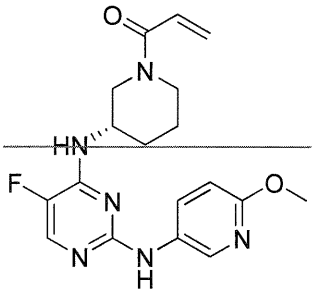
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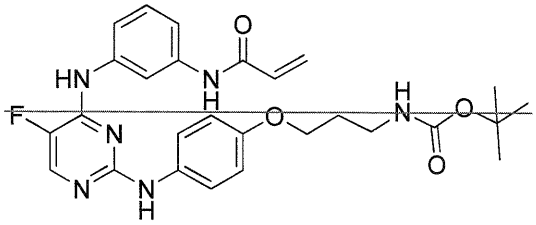
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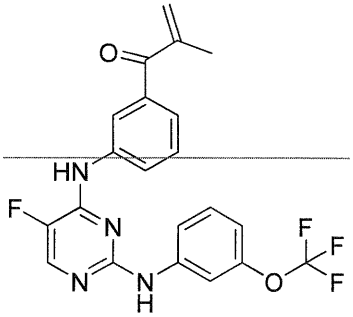
I-196



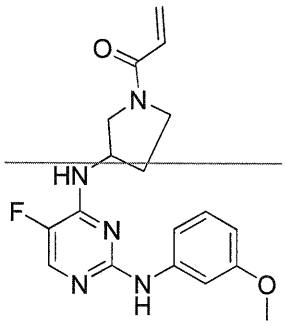
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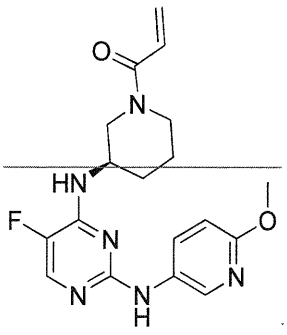
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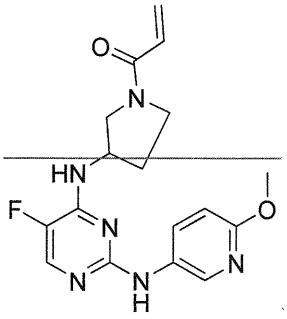
I-199



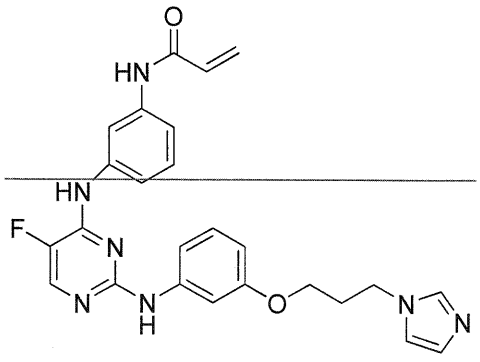
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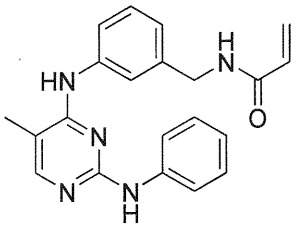
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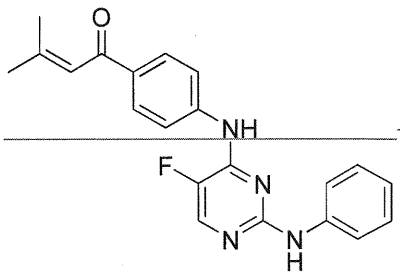
I-203



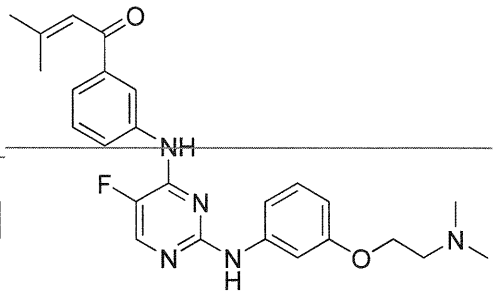
I-204



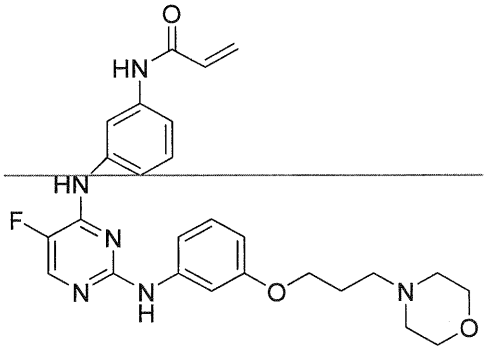
I-205



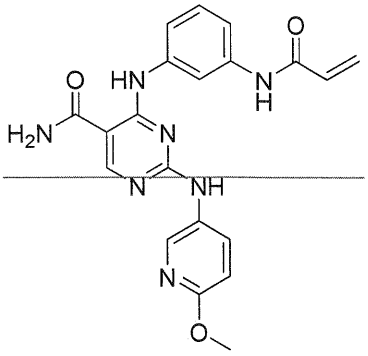
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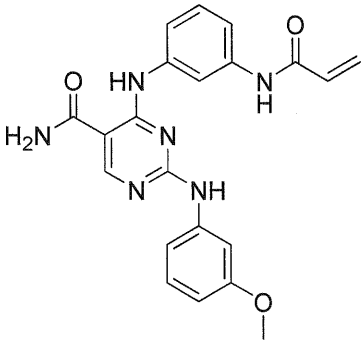
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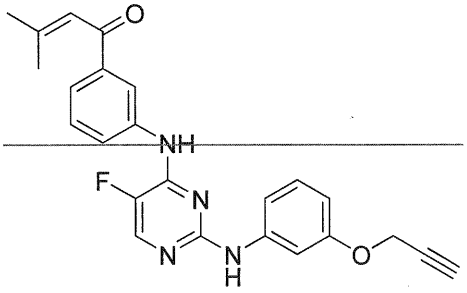
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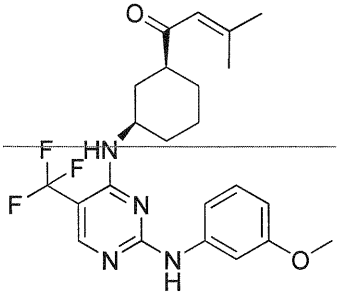
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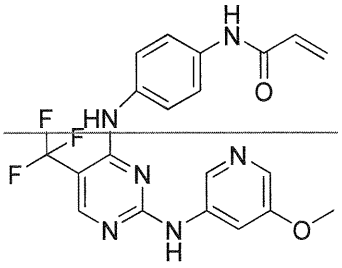
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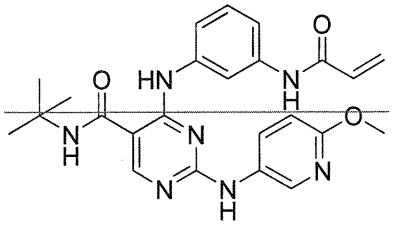
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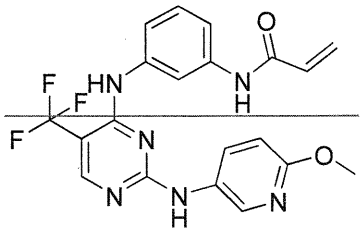
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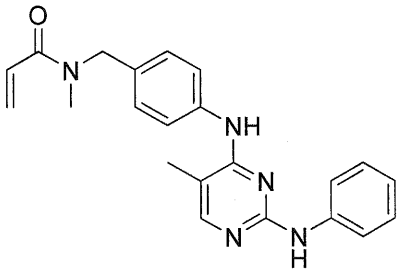
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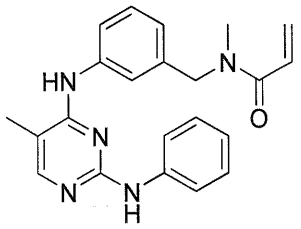
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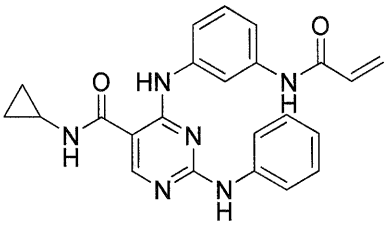
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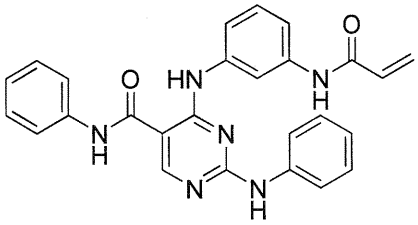
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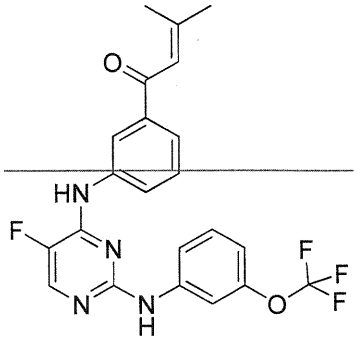
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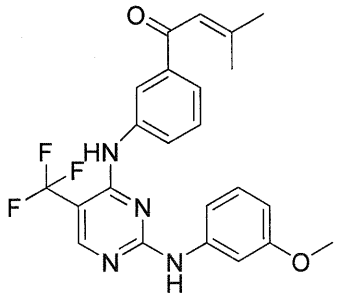
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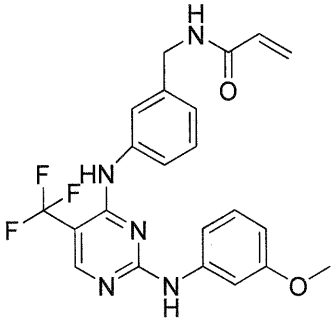
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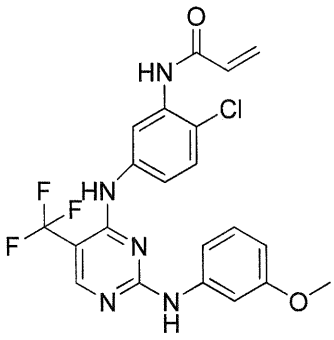
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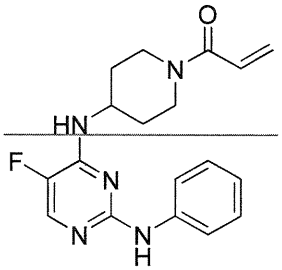
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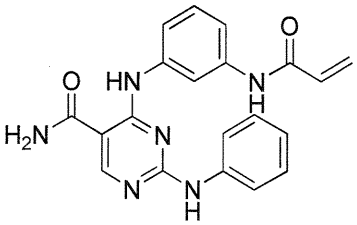
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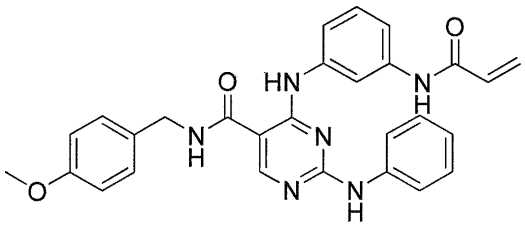
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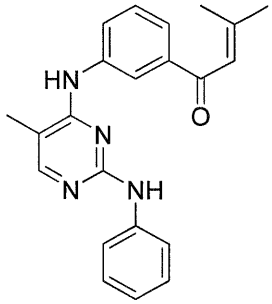
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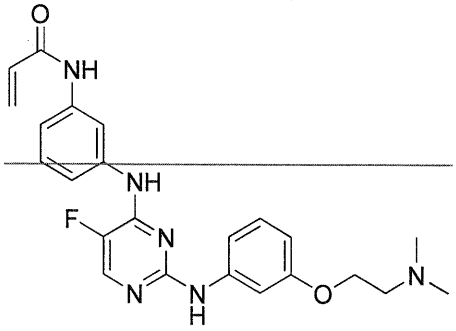
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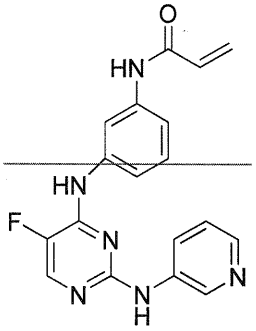
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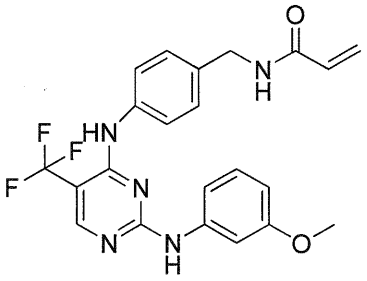
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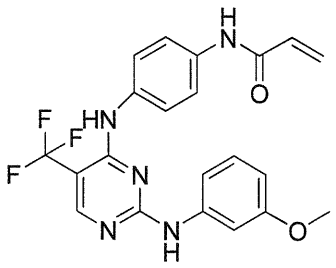
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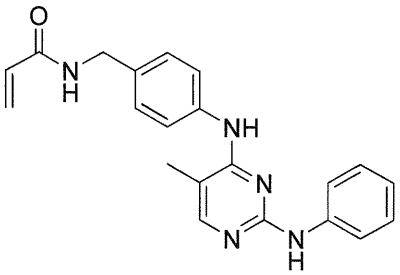
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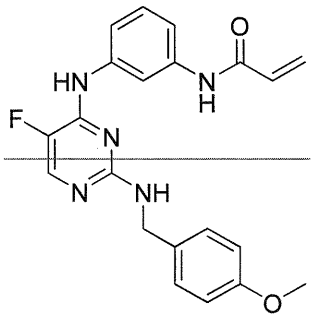
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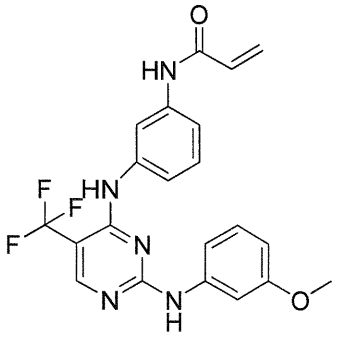
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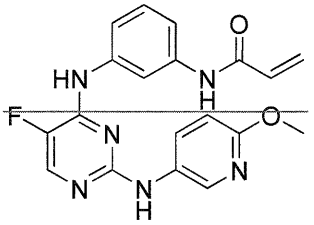
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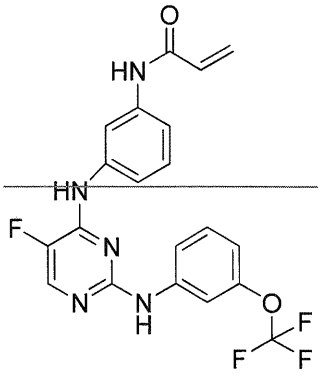
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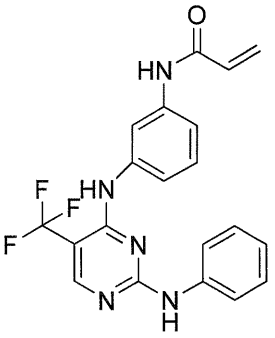
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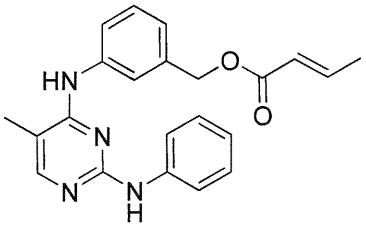
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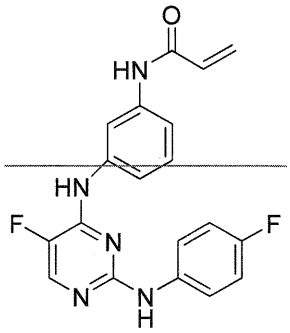
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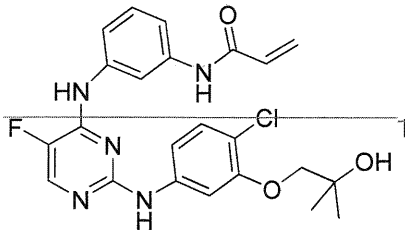
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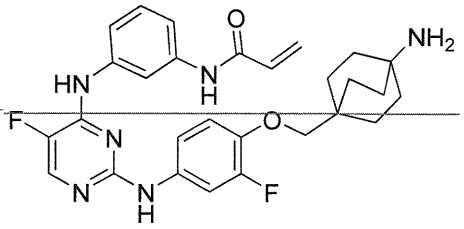
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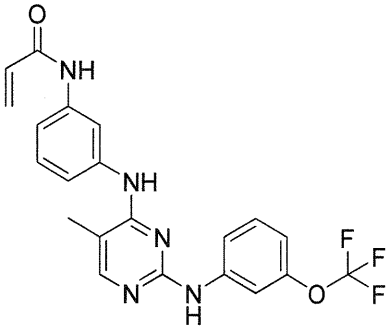
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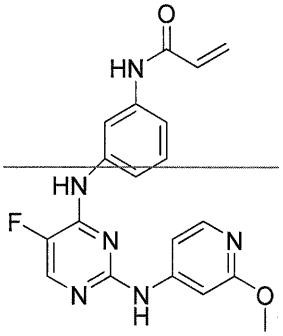
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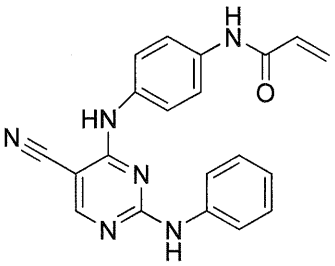
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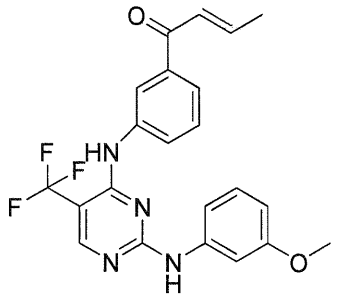
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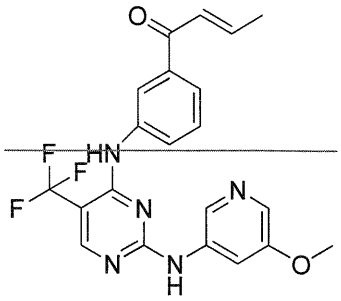
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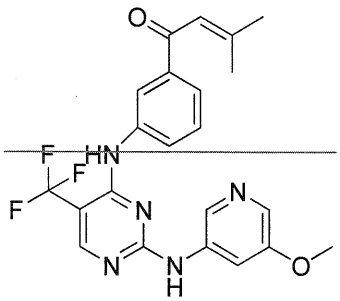
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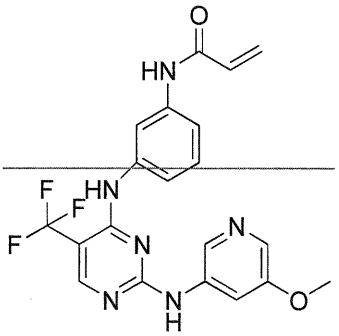
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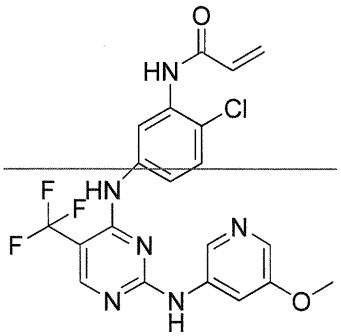
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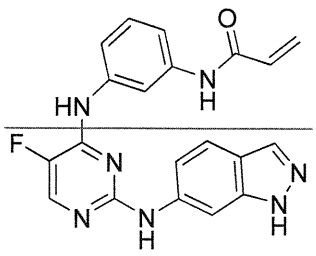
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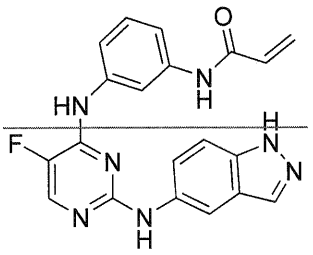
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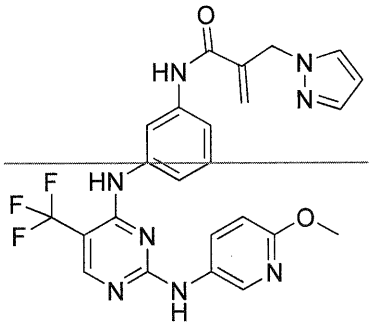
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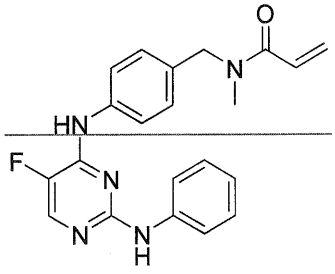
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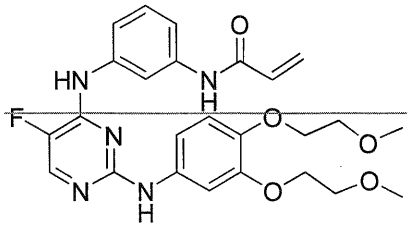
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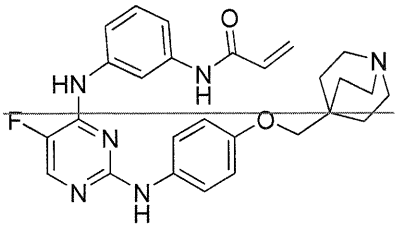
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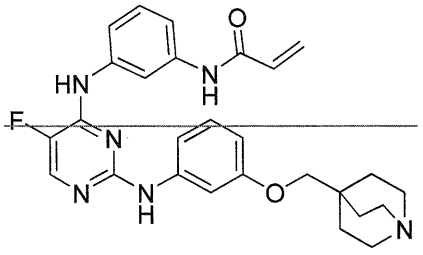
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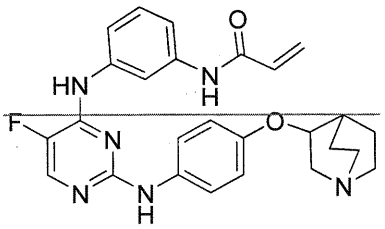
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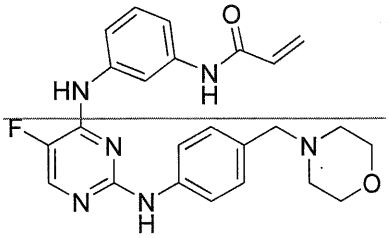
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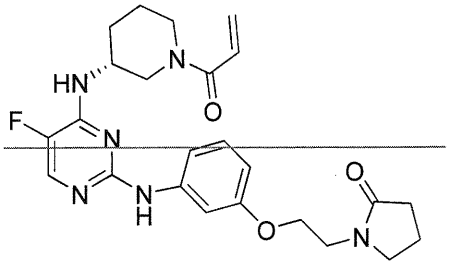
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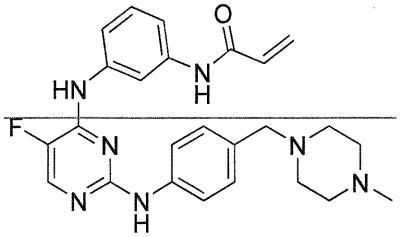
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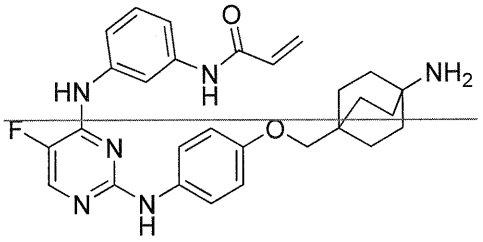
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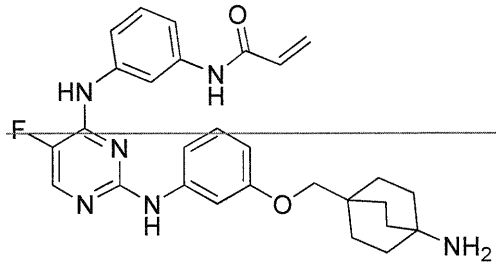
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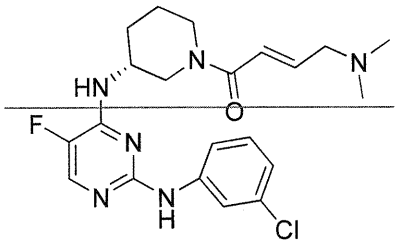
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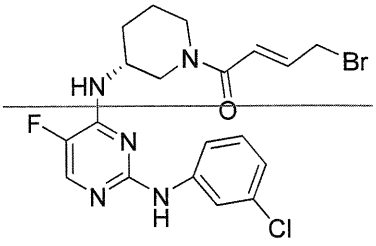
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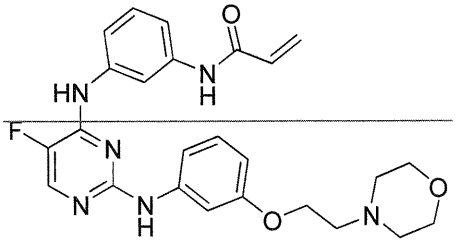
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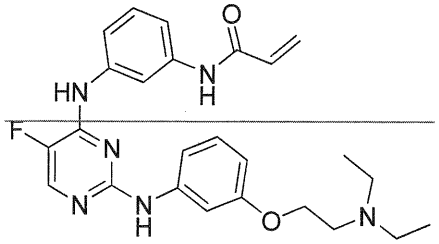
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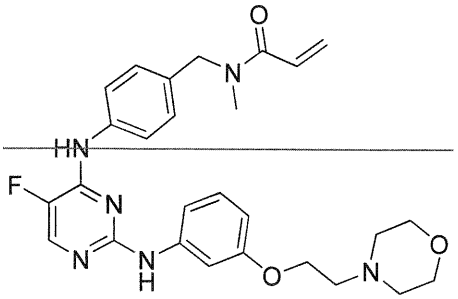
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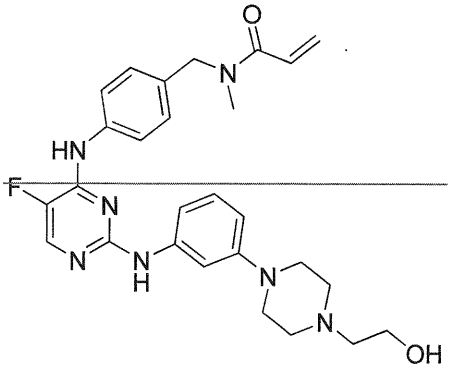
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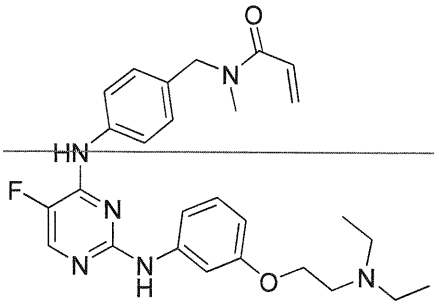
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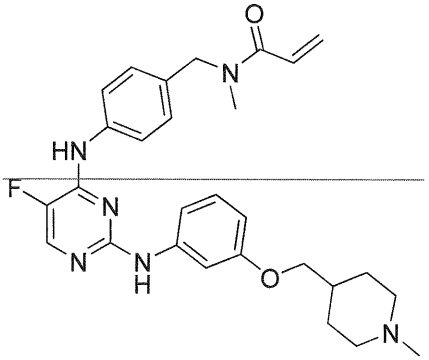
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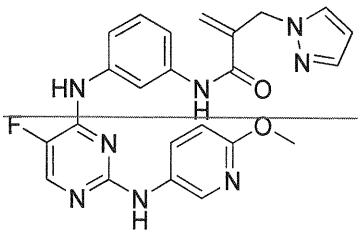
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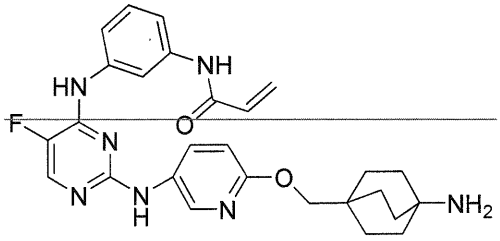
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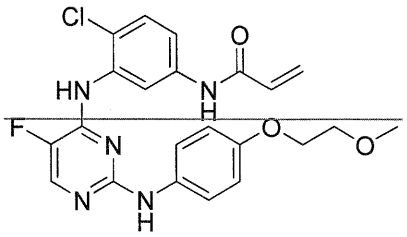
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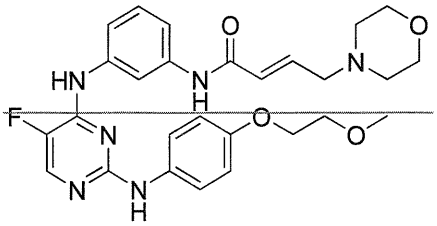
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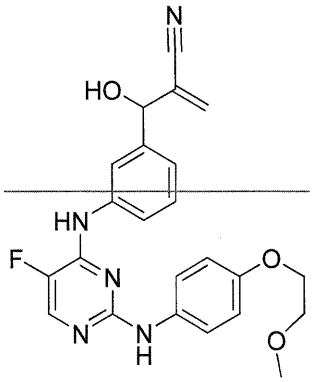
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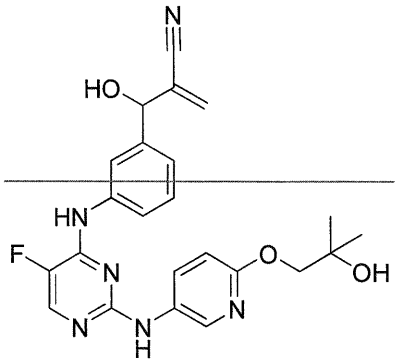
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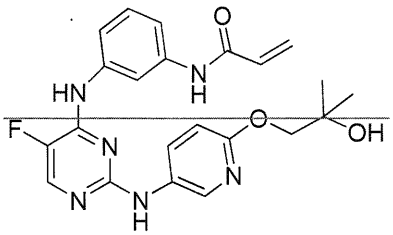
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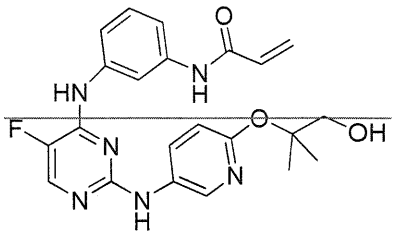
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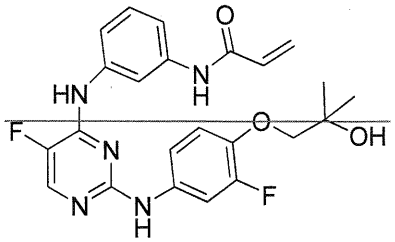
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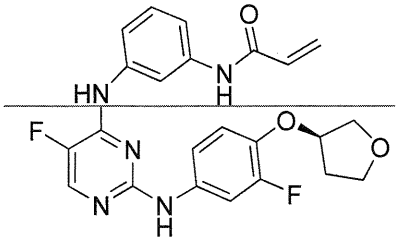
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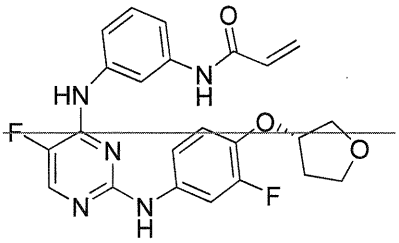
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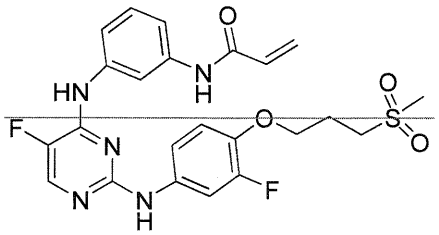
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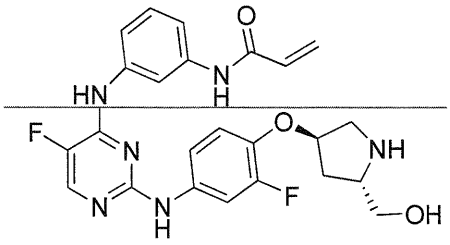
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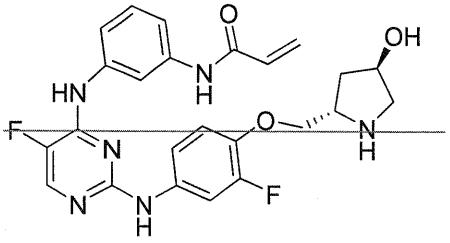
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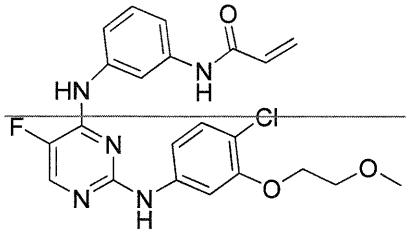
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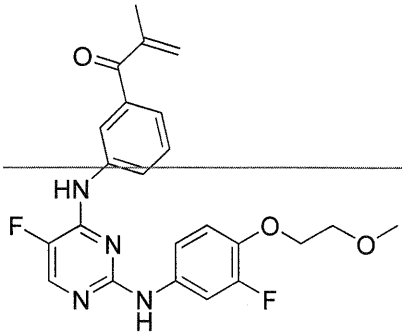
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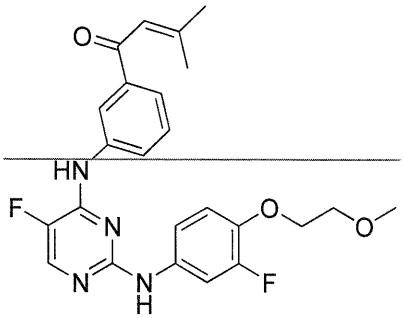
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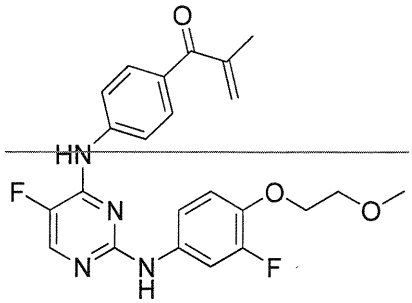
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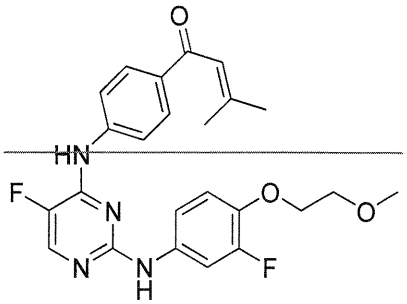
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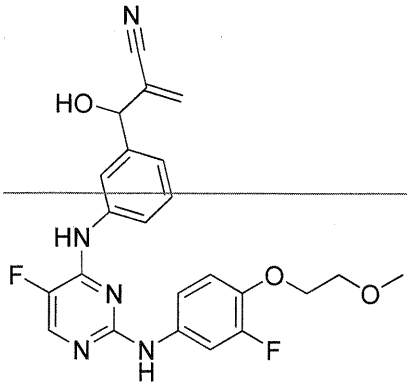
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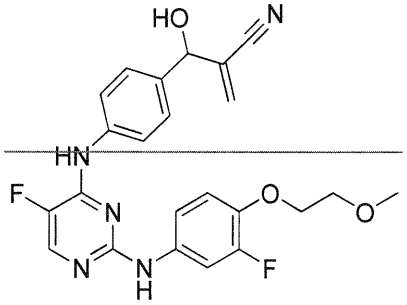
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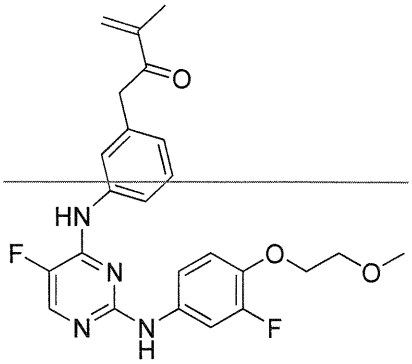
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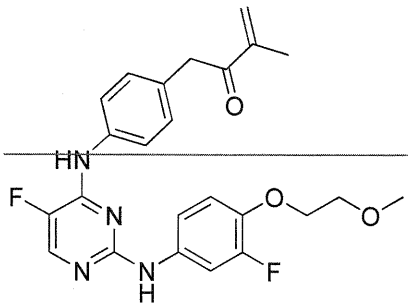
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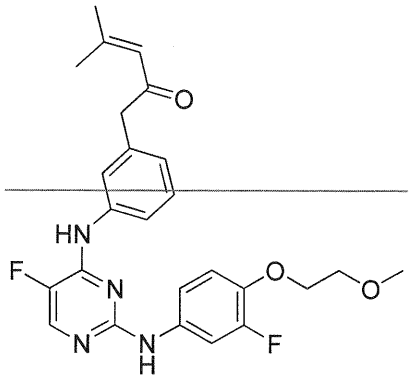
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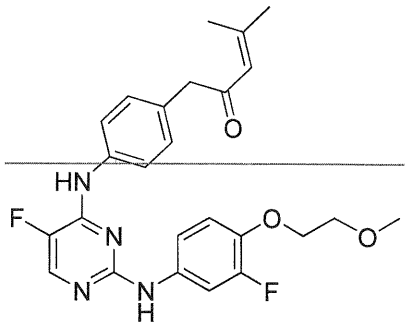
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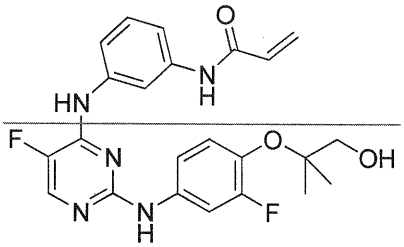
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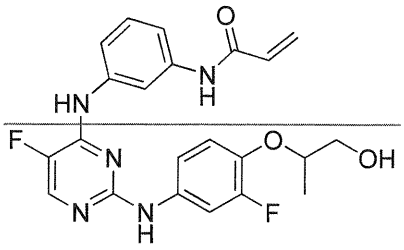
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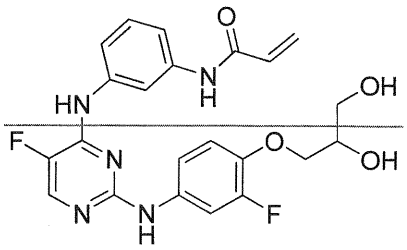
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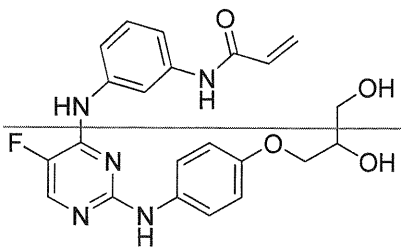
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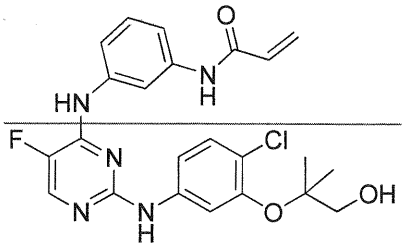
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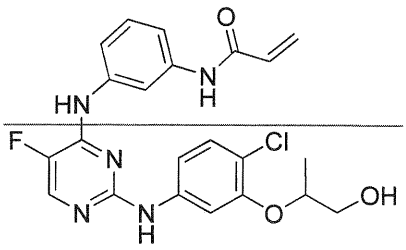
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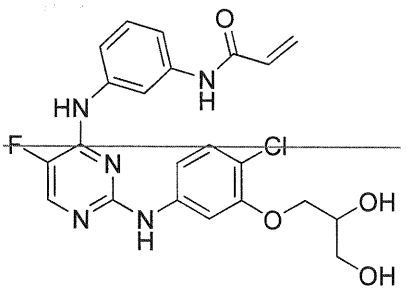
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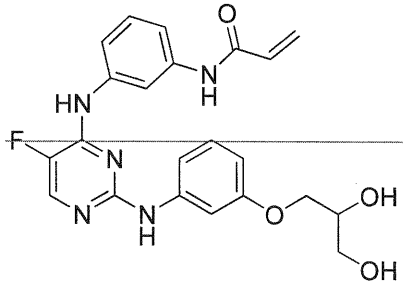
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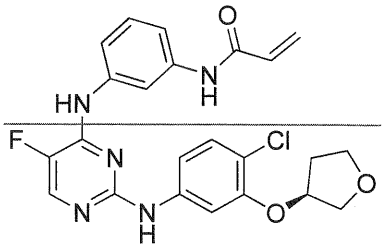
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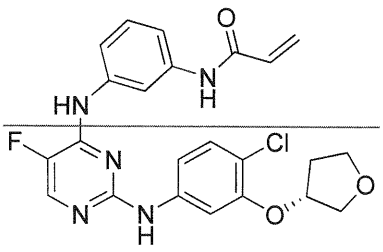
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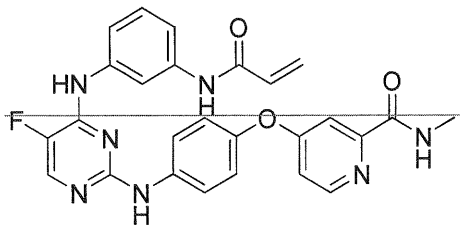
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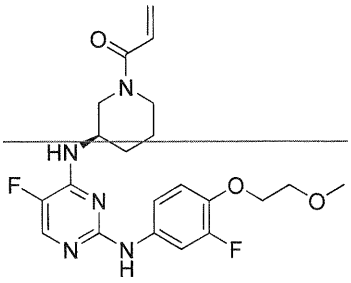
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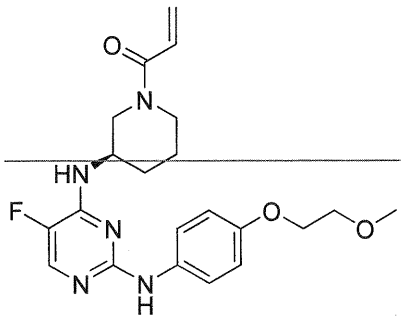
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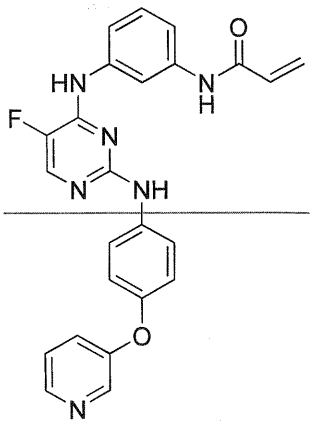
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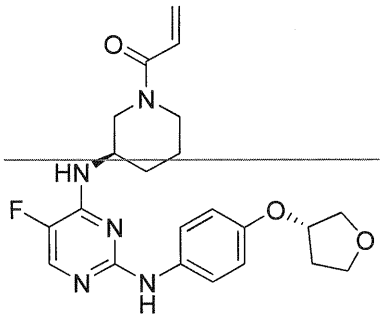
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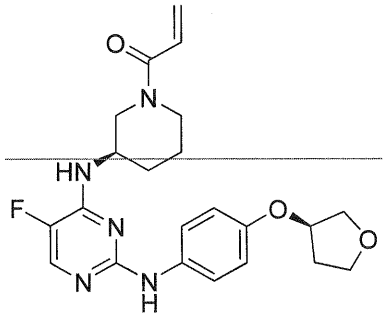
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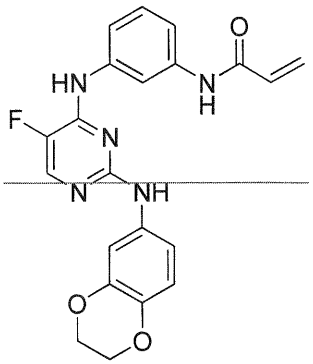
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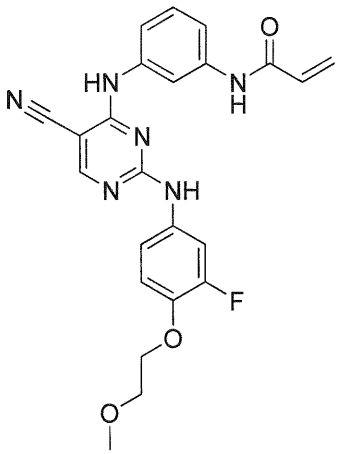
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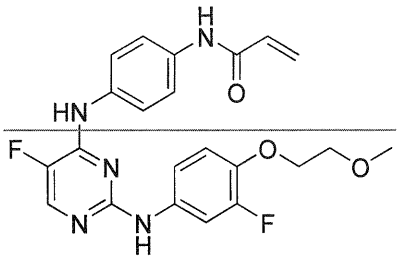
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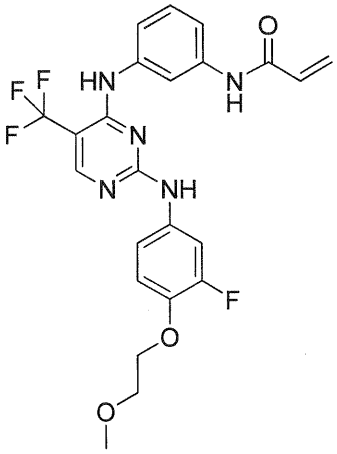
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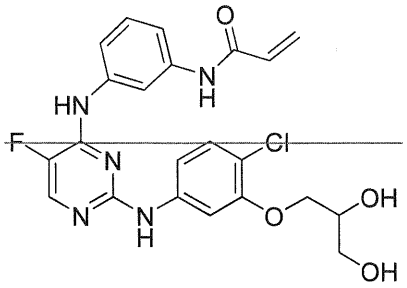
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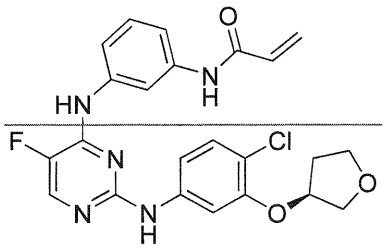
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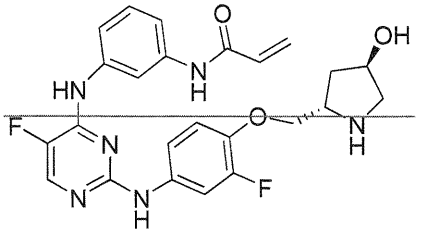
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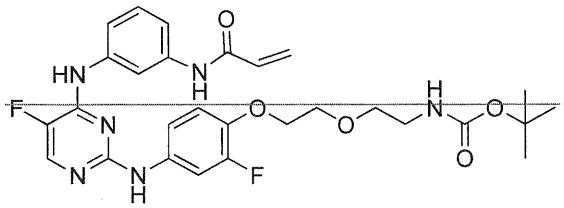
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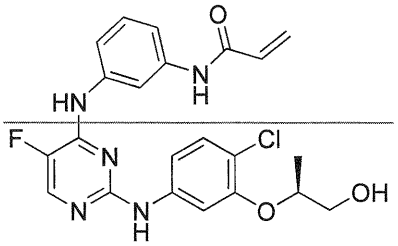
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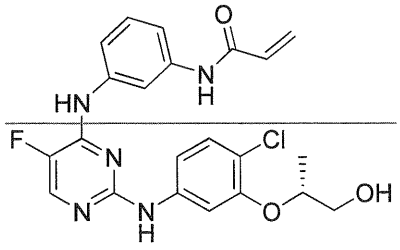
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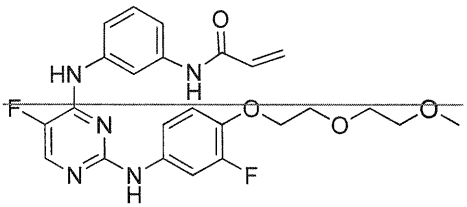
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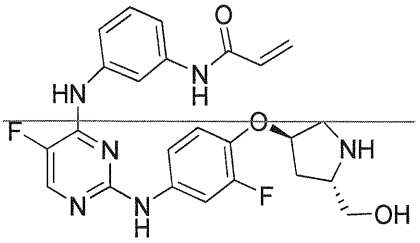
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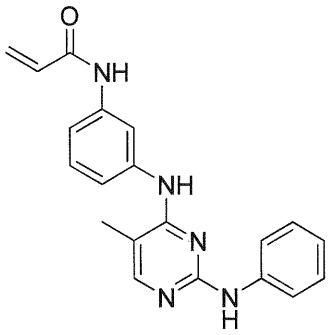
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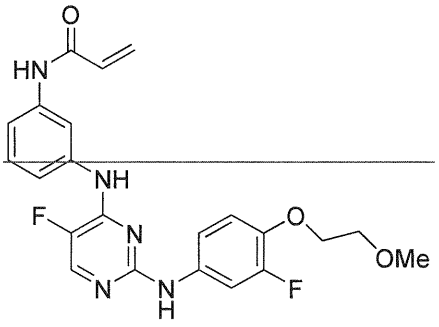
~~I-361,~~

or a pharmaceutically acceptable salt thereof.

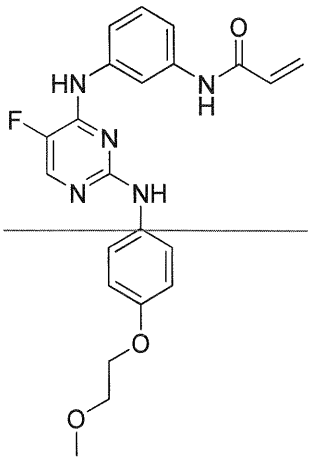
~~23~~21. The compound according to claim ~~22~~-20 having the structure:



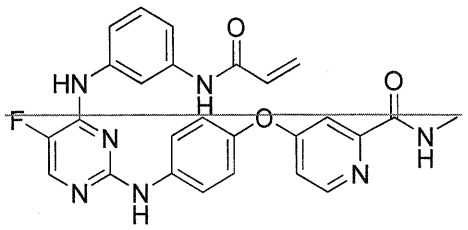
I-7



~~I-96~~



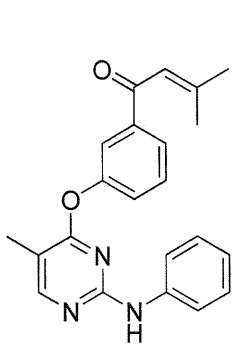
~~I-182~~



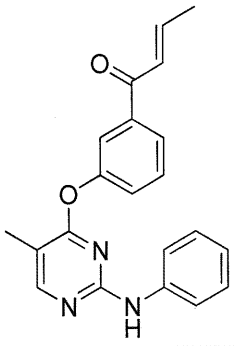
~~I-342~~

or a pharmaceutically acceptable salt thereof.

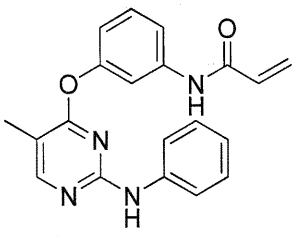
22. The compound according to claim 2 selected from the group consisting of:



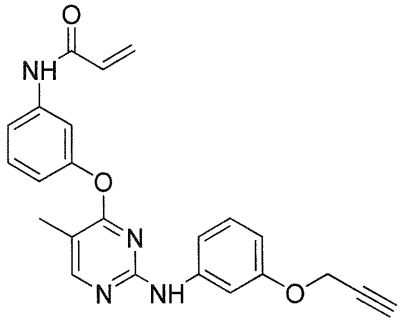
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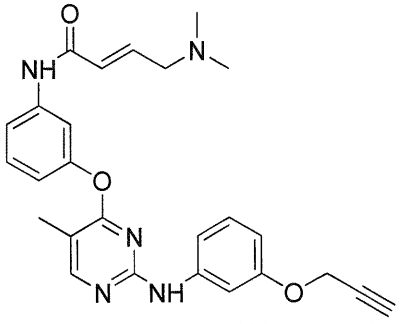
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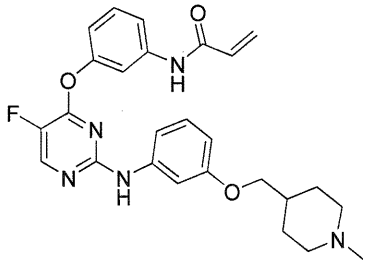
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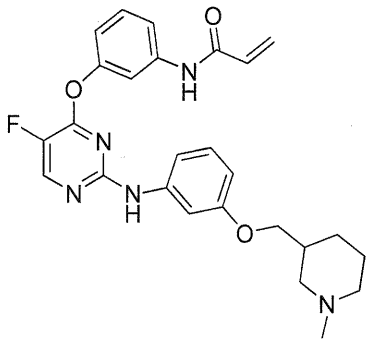
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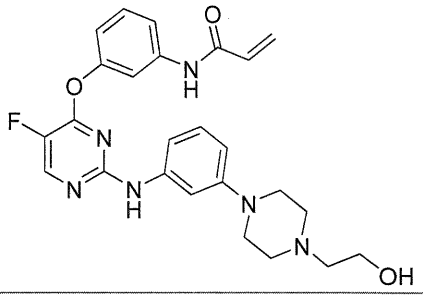
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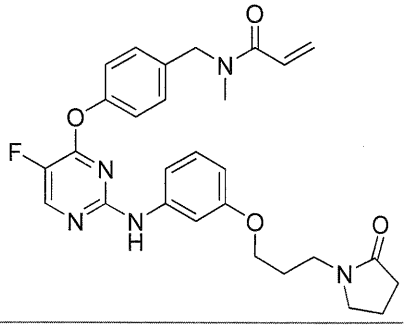
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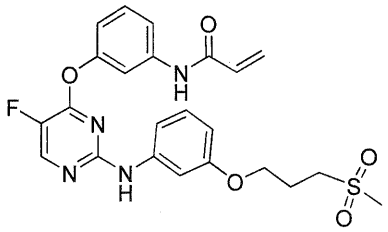
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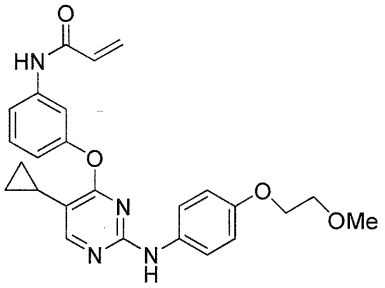
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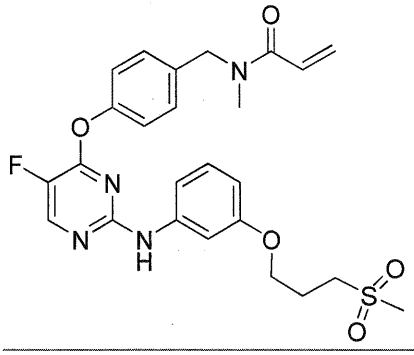
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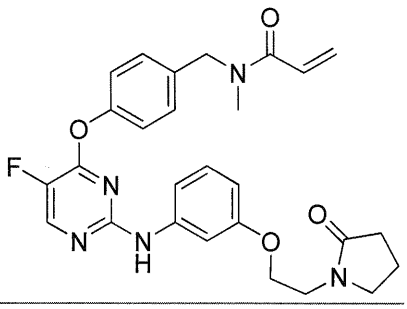
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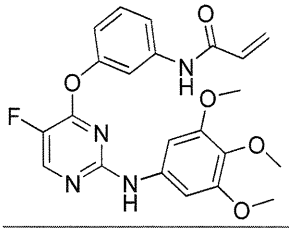
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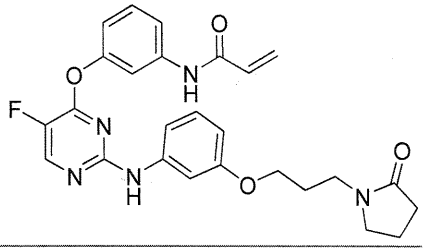
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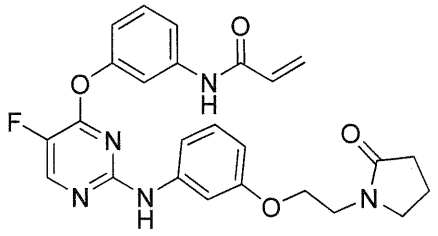
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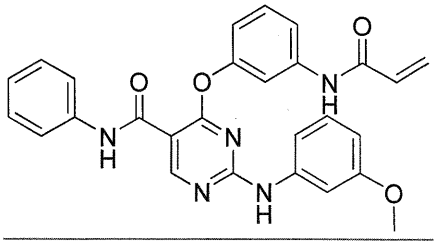
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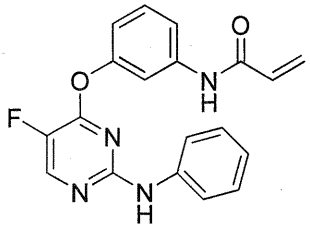
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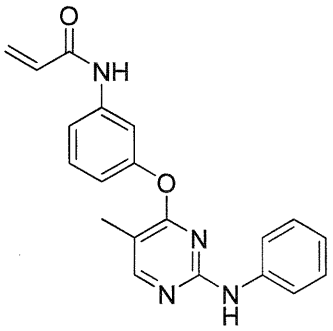
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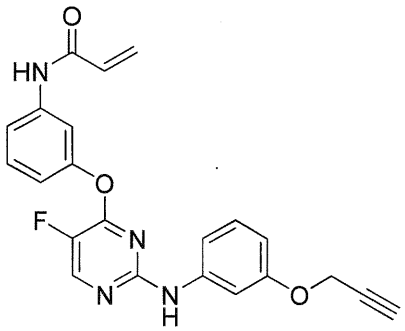
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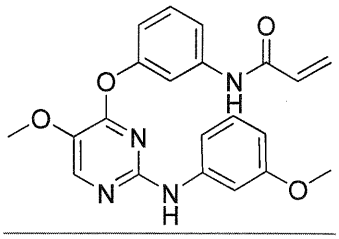
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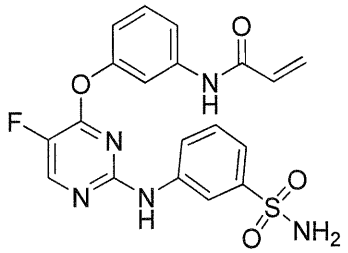
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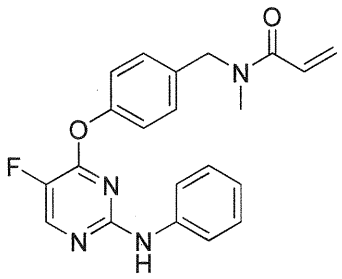
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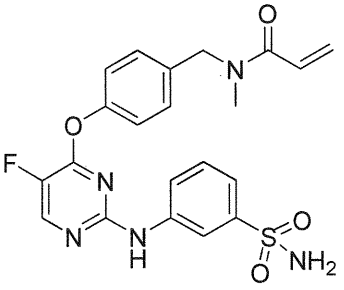


I-262

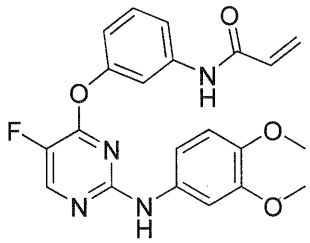


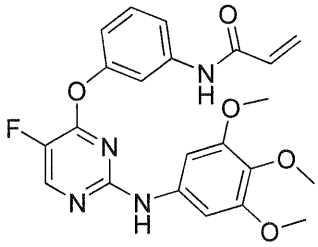
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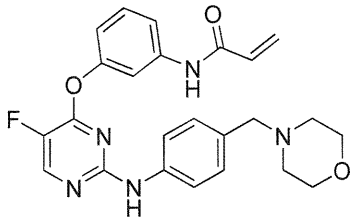


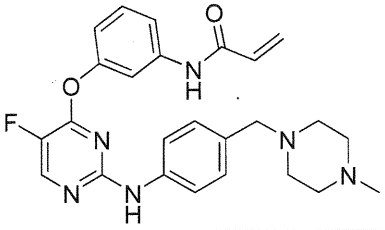
I-273 I-274



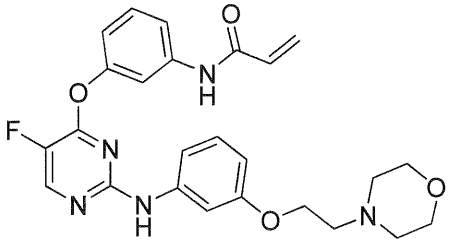


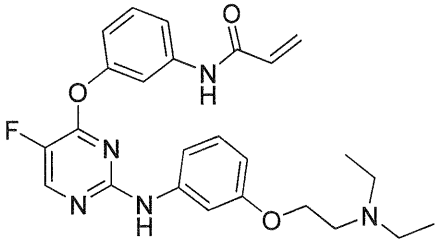
I-286 I-287





I-289 I-290





I-299 I-300

or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 1, wherein R^1 is –NHC(O)CH=CH_2.

24. The compound according to claim 23, wherein R^2 is hydrogen.

25. The compound according to claim 24, wherein Ring A is phenyl.

26. The compound according to claim 25, wherein Ring B is phenyl.

27. The compound according to claim 26, wherein at least one R^x is selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxyalkoxy, and halogen.

28. The compound according to claim 27, wherein at least one R^x is selected from methyl, methoxy, methoxyethoxy and fluoro.

29. The compound according to claim 1, wherein R is independently selected from hydrogen, C_{1-6} aliphatic, phenyl, 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.

30. The compound according to claim 2, wherein R^1 is $-NHC(O)CH=CH_2$.

31. The compound according to claim 30, wherein R^2 is hydrogen.

32. The compound according to claim 31, wherein Ring A is phenyl.

33. The compound according to claim 32, wherein Ring B is phenyl.

34. The compound according to claim 33, wherein at least one R^x is selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxyalkoxy, and halogen.

35. The compound according to claim 34, wherein at least one R^x is selected from methyl, methoxy, methoxyethoxy and fluoro.

36. The compound according to claim 2, wherein R is independently selected from hydrogen, C_{1-6} aliphatic, phenyl, 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.

~~24~~37. A composition comprising a compound according to claim 1, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

38. A composition comprising a compound according to claim 2, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

~~25~~39. The composition according to claim ~~24~~37, in combination with an additional therapeutic agent.

~~26~~40. The composition according to claim ~~25~~39, wherein the additional therapeutic agent is a chemotherapeutic agent.

~~27~~41. ~~The u~~Use of a compound according to claim 1 or claim 2 in the manufacture of a medicament for inhibiting activity of BTK, or a mutant thereof, in a patient or in a biological sample.

~~28~~42. The use according to claim ~~27~~41, wherein the activity of BTK, or a mutant thereof, ~~activity~~ is inhibited irreversibly.

~~29~~43. The use according to claim ~~28~~42, wherein the activity of BTK, or a mutant thereof, ~~activity~~ is inhibited irreversibly by covalently modifying Cys 481 of BTK.

~~30~~44. ~~The u~~Use of a compound according to claim 1 or claim 2 in the manufacture of a medicament for the treatment of a BTK-mediated disorder in a patient in need thereof.

~~31~~45. The use according to claim ~~30~~44, wherein the disorder is an autoimmune disease, a heteroimmune disease, an inflammatory disease, a cancer, a disease of the bone and joints, or a thromboembolic disorder.

~~32~~46. The use according to claim ~~31~~45, wherein the disorder is selected from rheumatoid arthritis, multiple sclerosis, B-cell chronic lymphocytic leukemia, acute lymphocytic leukemia, hairy cell leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, bone cancer, bone metastasis, osteoporosis, irritable bowel syndrome, Crohn's disease, lupus, or disorders associated with renal transplant.

~~33~~47. ~~The u~~Use of a compound according to claim 1 or claim 2 for the preparation of a medicament for inhibiting one or more TEC-kinases, or a mutant thereof, activity in a patient or in a biological sample.

~~34~~48. The use according to claim ~~33~~47, wherein the activity of the TEC-kinase, or a mutant thereof, ~~activity~~ is inhibited irreversibly.

~~35~~49. The use according to claim ~~34~~ 48 wherein the TEC-kinase is selected from one or more of TEC, ITK or BMX.

~~36~~50. The use according to claim ~~35~~49, where the activity of the one or more of TEC, ITK or BMX ~~activity~~ is inhibited irreversibly by ~~eolvalently~~ covalently modifying Cys 449 of TEC, Cys 442 of ITK or Cys 496 of BMX.

~~37~~51. ~~The u~~Use of a compound according to claim 1 or 2 for the preparation of a medicament for the treatment of a TEC-kinase-mediated disorder in a patient in need thereof.

~~38~~52. The use according to claim ~~37~~51, wherein the disorder is an autoimmune disorder, an inflammatory disorder, a proliferative disorder, a hyperproliferative disease, an immunological-mediated diseases, a disease of the respiratory tract, a disease of the bone and joints, a skin disorder, a gastrointestinal disorder, a systemic disease, or allograft rejection.

~~39~~53. The use of a compound according to claim 1 or claim 2 for the preparation of a medicament for inhibiting one or more of ErbB1, ErbB2, ErbB3, or ErbB4, or a mutant thereof, activity in a patient or in a biological sample.

~~40~~54. The use according to claim ~~39~~53, wherein the activity of the one or more of ErbB1, ErbB2, or ErbB4, or a mutant thereof, ~~activity~~ is inhibited irreversibly.

~~41~~55. The use according to claim ~~40~~54, wherein the activity of the one or more of ErbB1, ErbB2, or ErbB4, or a mutant thereof, ~~activity~~ is inhibited irreversibly by covalently modifying Cys797 of ErbB1, Cys805 of ErbB2 or Cys803 of ErbB4.

~~42~~56. ~~The u~~Use of a compound according to claim 1 or claim 2 for the preparation of a medicament for the treatment of an ErbB1-, ErbB2-, ErbB3-, or ErbB4-mediated disorder in a patient in need thereof.

~~43~~57. The use according to claim ~~42~~56, wherein the disorder is a carcinoma selected from breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, bladder cancer, non-small cell lung cancer, squamous cell carcinoma, salivary gland carcinoma, ovarian carcinoma, or pancreatic cancer.

~~44~~58. The use according to claim ~~43~~57, wherein the disorder is selected from neurofibromatosis type I (NF1), neurofibromatosis type II (NF2) Schwann cell neoplasms, or a Schwannoma.

~~45~~59. Use of a compound according to claim 1 or claim 2 for the preparation of a medicament for inhibiting JAK3, or a mutant thereof.

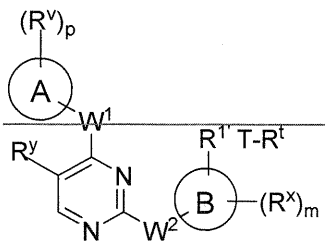
~~46~~60. The use according to claim ~~45~~59, wherein the activity of JAK3, or a mutant thereof, ~~activity~~ is inhibited irreversibly.

~~47~~61. The use according to claim ~~46~~60, wherein the activity of JAK3, or a mutant thereof, ~~activity~~ is inhibited irreversibly by covalently modifying Cys 909 of JAK3.

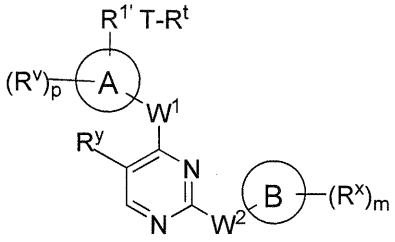
~~48~~62. ~~The u~~Use of a compound according to claim 1 or claim 2 for preparation of a medicament for treating a JAK3-mediated disorder in a patient in need thereof.

4963. The use according to claim 4862, wherein the disorder is selected from an autoimmune disorder, an inflammatory disorder, a neurodegenerative disorder, or a solid or hematologic malignancy.

5064. A compound of formula ~~V-a or~~ **V-b**:



~~V-a~~



V-b,

wherein:

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

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

$R^{1'}$ is a bivalent warhead group –L-Y, wherein $R^{1'}$ is attached to an atom other than an atom adjacent to the atom attached to W^1 on Formula **V-b** ~~or W^2 on Formula V-a~~:

L is a covalent bond or a bivalent C_{1-8} straight or branched, hydrocarbon chain, wherein L has at least one double bond and one or two additional units of L are optionally and independently replaced by cyclopropylene, –NR-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-,-SO_2N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(=S)-, -C(=NR)-, -N=N-, or -C(=N_2)-;

Y is a bivalent group selected from 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; and

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

Q is a covalent bond or 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

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

R^y is hydrogen, halogen, CN, CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, -OR, -C(O)R, or -C(O)N($R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocylic 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;

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by -NR^2-, -N(R^2)C(O)-, -C(O)N(R^2)-, -N(R^2)SO_2-, -SO_2N(R^2)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R~~, or:~~

~~R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or~~

~~R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated,~~

~~partially unsaturated, or aromatic fused ring;~~

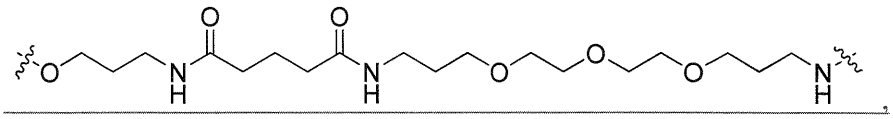
m and p are independently 0-4;

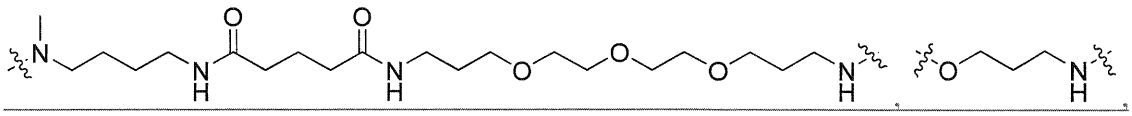
R^x and R^y are independently selected from -R, halogen, –OR, $-O(CH_2)_qOR$, –CN, $–NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $–C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1-4~~; or:~~

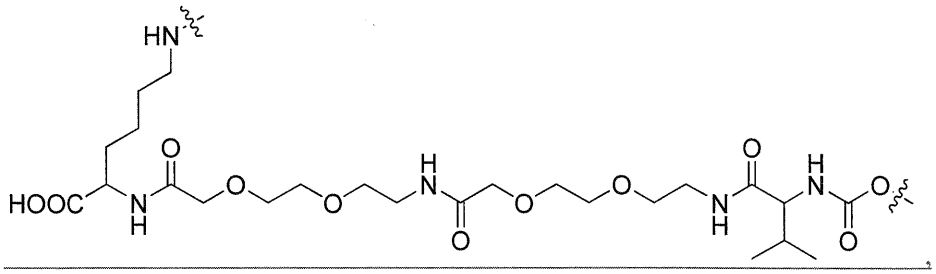
~~R^* and $R^{1'}$ when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, CN, or C_{1-6} aliphatic; or~~

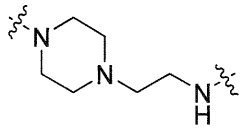
~~R^y and $R^{1'}$ when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, CN, or C_{1-6} aliphatic;~~

T is ~~a bivalent tethering moiety selected from a covalent bond, a polymer, a water soluble polymer, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkenyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkylalkenylalkyl~~ selected from

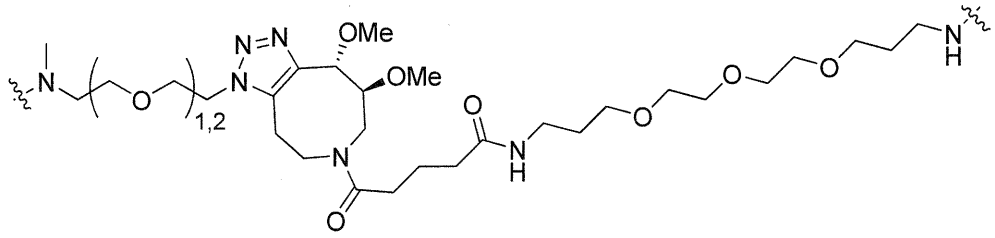








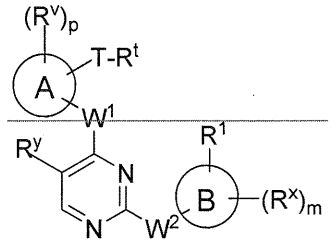
or



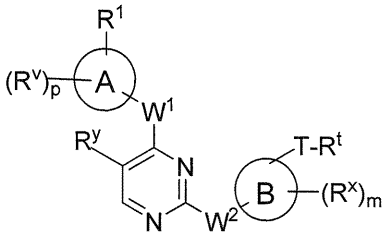
; and

R^t is a detectable moiety selected from a radioisotope, a biotin, or a fluorescent label~~, a mass tag, a chemiluminescent group, a chromophore, an electron dense group or an energy transfer agent~~.

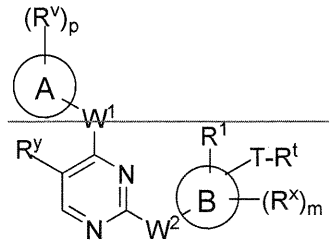
~~5165~~. A compound of formula ~~VI-a,~~ **VI-b**~~, VII-a,~~ or **VII-b**:



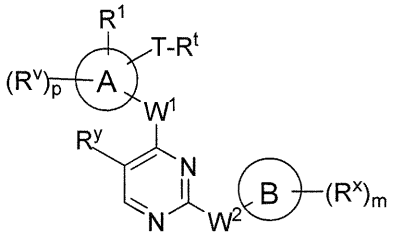
~~VI-a~~



VI-b



~~VII-a~~



VII-b,

wherein:

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

Ring B is an optionally substituted ~~group selected from~~ phenyl~~, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl 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 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or~~

~~sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur~~;

R^1 is a warhead group–L-Y selected from the following (a), (b), (c), (h), (k), (l), (m), (n), (o), and (p) combinations of –L- and –Y, and wherein R^1 is attached to an atom other than an atom adjacent to the atom attached to W^1 on Formula VI-b or VII-b:

(a) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two ~~additional~~ 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 Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(b) 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 or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(c) 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 or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(h) 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 or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(k) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one or two additional methylene units of L are 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 Y C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(l) L is a covalent bond and Y is selected from:

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

(*ii*) C_{2-6} alkenyl 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

(*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

(*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

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

(*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;

(m) L is –C(O)- and Y 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

(*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

(*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

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

(*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;

(n) L is –N(R)C(O)- and Y 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

(*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

(*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

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

(*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;

(o) L is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and Y is selected from:

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

(*ii*) C_{2-6} alkenyl 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

(*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

(*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

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

(p) L is a covalent bond, $-CH_2-$, -NH-, -C(O)-, $-CH_2NH-$, $-NHCH_2-$, –NHC(O)-, $-NHC(O)CH_2OC(O)-$, $-CH_2NHC(O)-$, $-NHSO_2-$, $-NHSO_2CH_2-$, ~~$-NHC(O)CH_2OC(O)-$,~~ or $-SO_2NH-$; and Y 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

(*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

(*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

(*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

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

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

R^y is hydrogen, halogen, CN, CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, -OR, -C(O)R, or -C(O)N$(R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocylic 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;

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by -NR^2-, -N(R^2)C(O)-, -C(O)N(R^2)-, -N(R^2)SO_2-, -SO_2N(R^2)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R~~, or:~~

~~R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or~~

~~R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring~~;

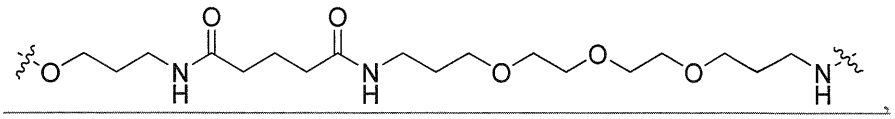
m and p are independently 0-4;

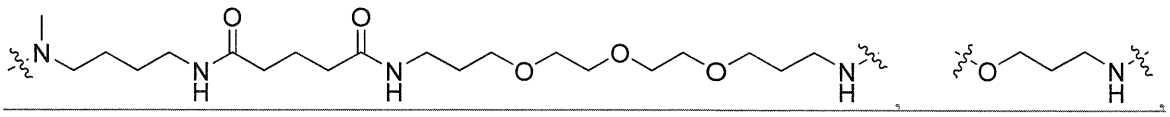
R^x and R^v are independently selected from -R, halogen, –OR, $-O(CH_2)_qOR$, –CN, $–NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $–C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1-4~~; or:~~

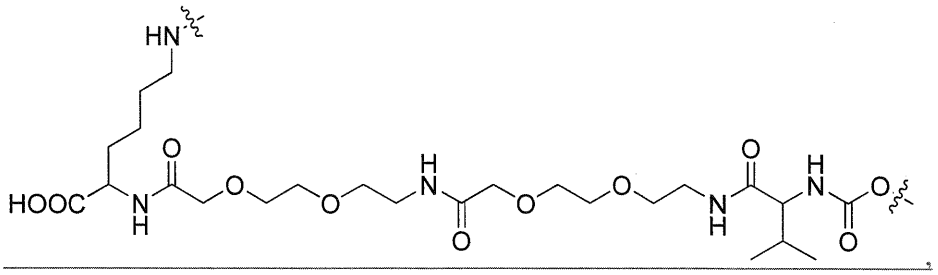
~~R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, CN, or C_{1-6} aliphatic; or~~

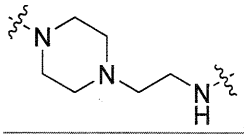
~~R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, CN, or C_{1-6} aliphatic~~;

T is ~~a bivalent tethering moiety selected from a covalent bond, a polymer, a water soluble polymer, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkenyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkylalkenylalkyl~~ selected from

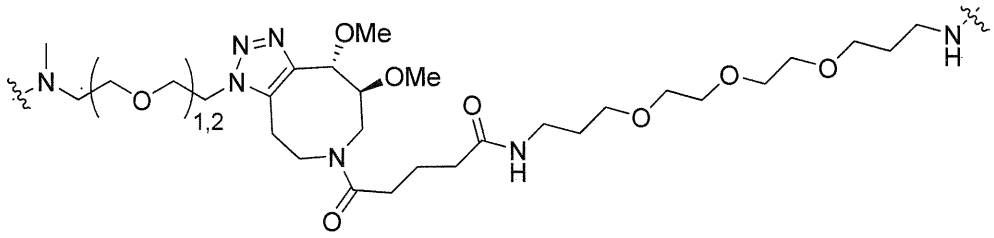








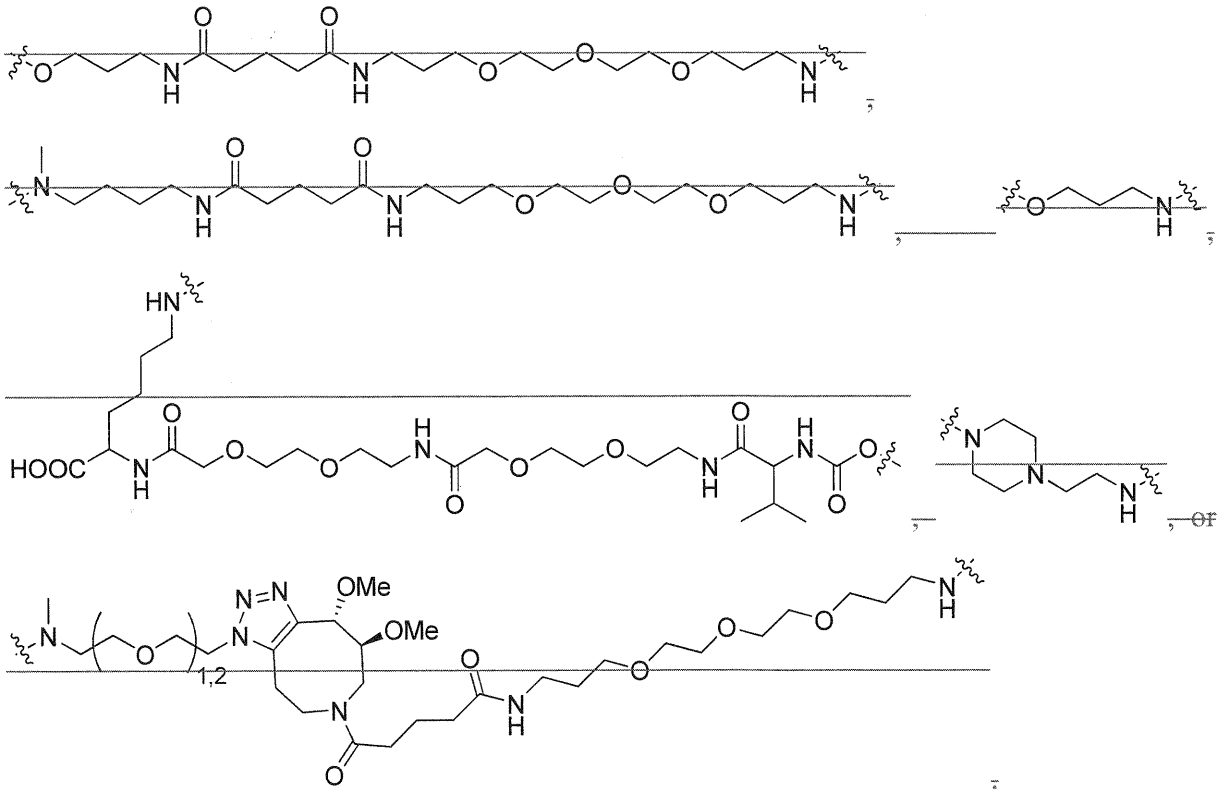
or



; and

R^t is a detectable moiety selected from a radioisotope, a biotin, or a fluorescent label~~, a mass tag, a chemiluminescent group, a chromophore, an electron dense group or an energy transfer agent~~.

~~52. The compound of claim 50 or 51, wherein T is selected from:~~



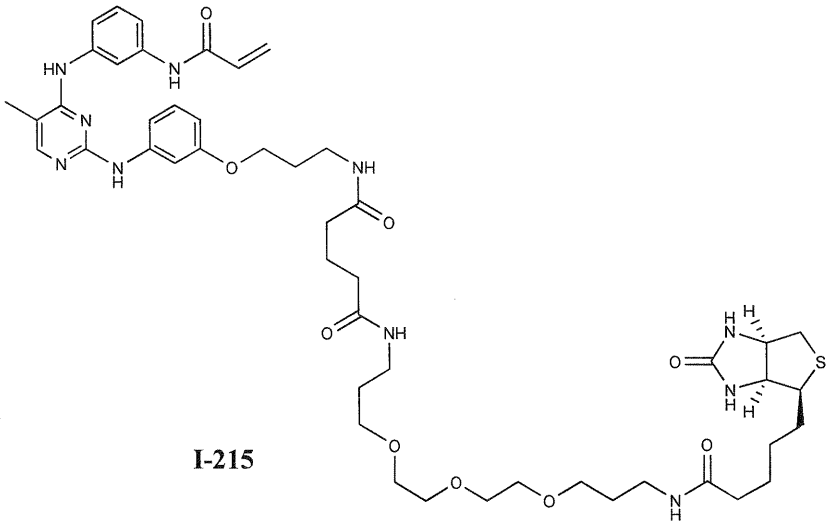
5366. The compound of claim ~~50 or 51~~64 or 65, wherein R^t is biotin.

5467. The compound of claim ~~50 or 51~~64 or 65, wherein R^t is biotin sulfoxide.

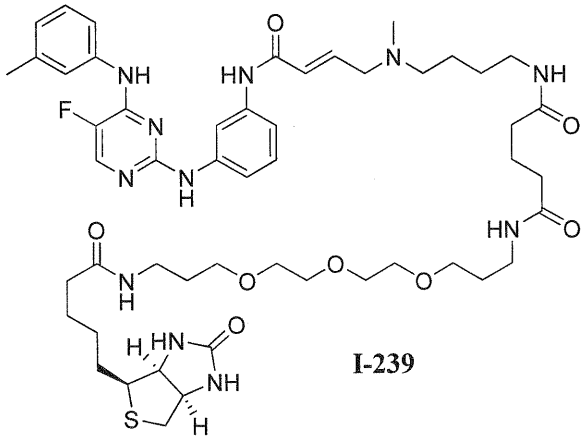
5568. The compound of claim ~~50 or 51~~64 or 65, wherein R^t is a radioisotope.

5669. The compound of claim ~~50 or 51~~64 or 65, wherein R^t is a fluorescent label.

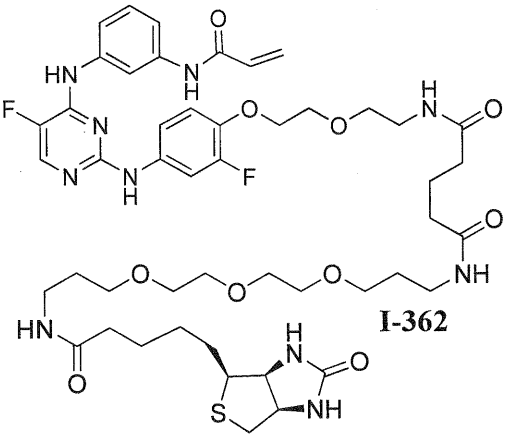
~~57~~70. The compound of claim ~~50~~ 64 or 65 having the structure:



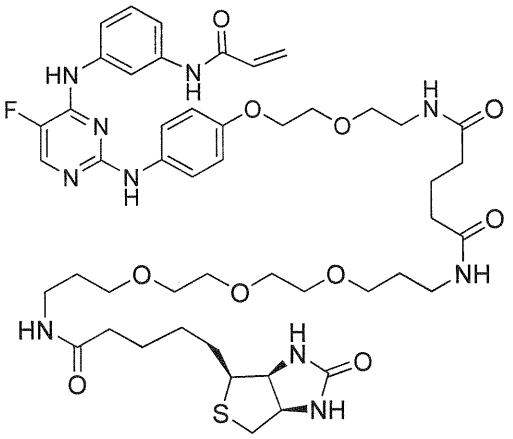
I-215



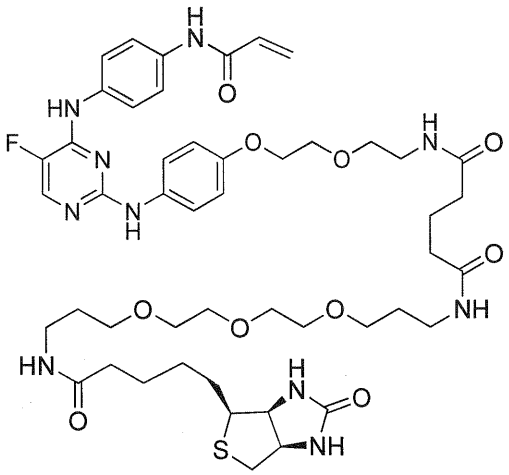
I-239



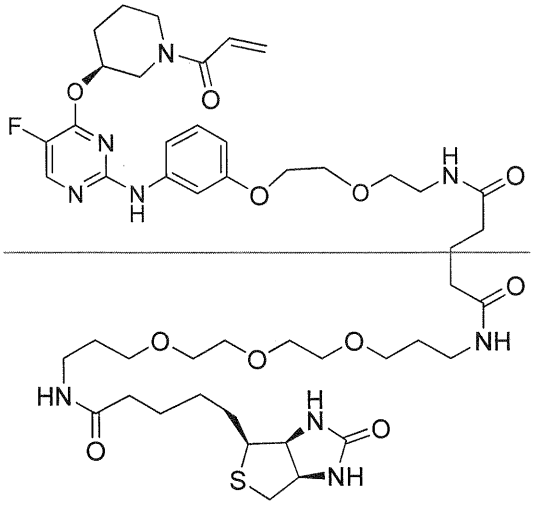
I-362



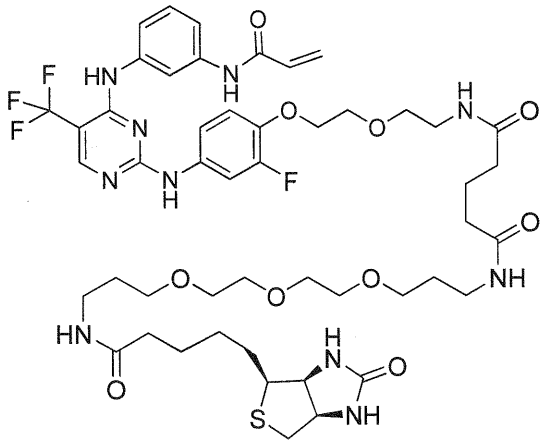
I-363



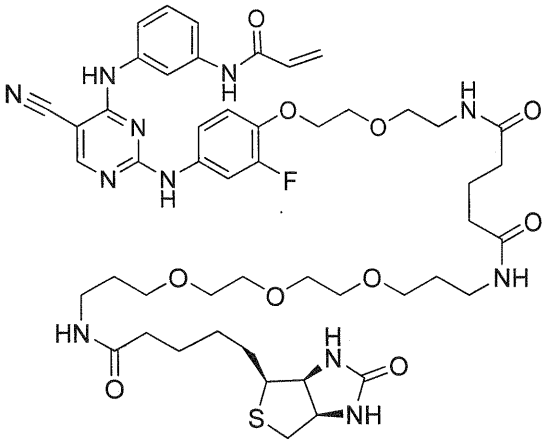
I-364



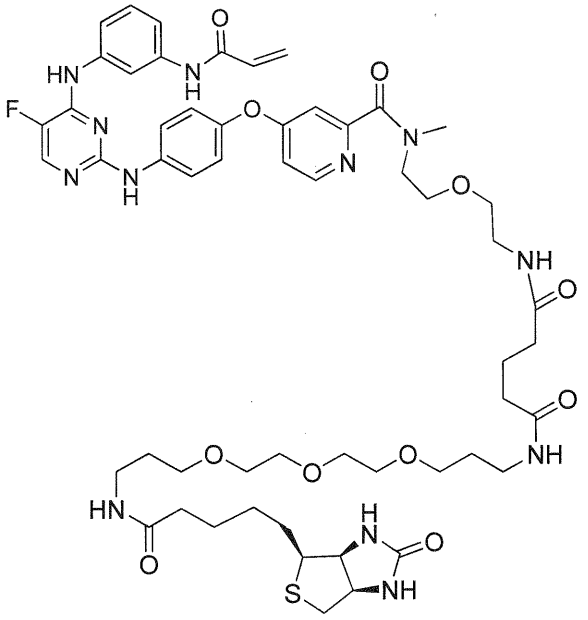
~~I-365~~



I-366



I-367



or **I-368.**

~~59~~71. A method comprising the steps of:

(a) providing one or more tissues, cell types, or a lysate thereof, obtained from a patient administered at least one dose of a compound according to claim 1,

(b) contacting said tissue, cell type, or a lysate thereof, with a different compound according to claim 1, tethered to a detectable moiety to form a probe compound, to covalently modify at least one protein kinase present in said tissue, cell type, or a lysate thereof; and

(c) measuring the amount of said protein kinase covalently modified by the probe compound to determine occupancy of said protein kinase by said compound according to claim 1 as compared to occupancy of said protein kinase by said probe compound.

~~60~~72. The method of claim ~~59~~71, further comprising the step of adjusting the dose of the compound according to claim 1 to increase occupancy of the protein kinase.

~~61~~73. The method of claim ~~59~~71, further comprising the step of adjusting the dose of the compound according to claim 1 to decrease occupancy of the protein kinase.

~~62~~74. The method of claim ~~59~~71, wherein the measuring step is carried out by one of the following: flow cytometry, Western blot, or ELISA.