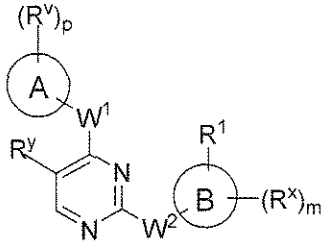
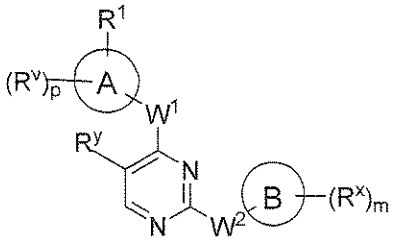
[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY ~~OF THE INVENTION~~

[0006] It has now been found that compounds of the present disclosure~~this invention~~, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of one or more protein kinases. Such compounds have general formulae **I-a** and **I-b**:



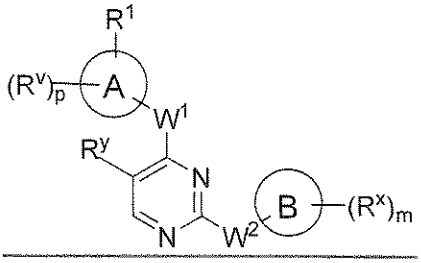
I-a



I-b

or a pharmaceutically acceptable salt thereof, wherein Ring A, Ring B, m, p, R^x, R^y, R^v, W^1, W^2, and R^1 are as defined herein.

[0006a] In a first aspect of the present disclosure, there is provided a compound of formula I-b:

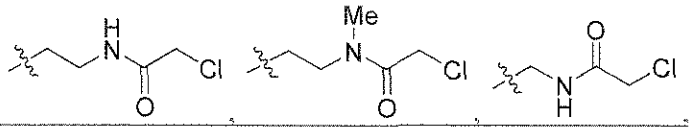


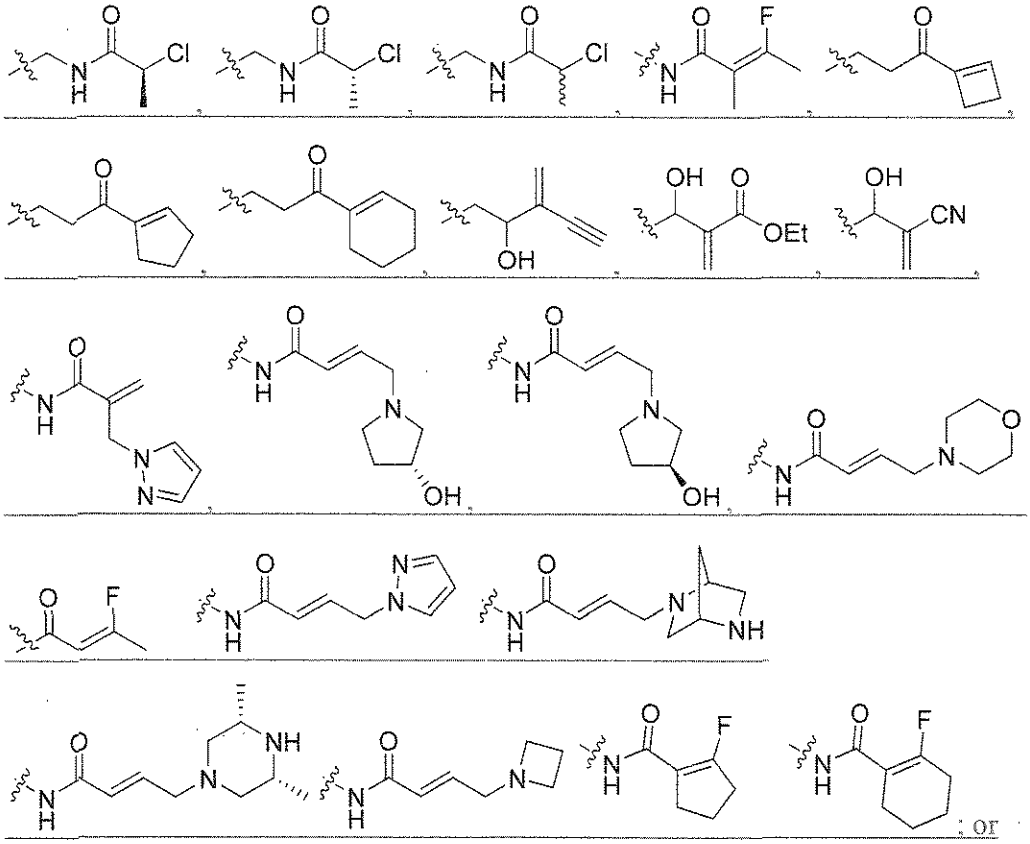
I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted phenyl;

Ring B is an optionally substituted phenyl;

R^1 is a warhead group selected from 



; or

R^1 is a warhead group –L-Y selected from the following combinations of –L- and –Y, wherein R^1 is attached to an atom other than an atom adjacent to the atom attached to W^1 on Formula I-b:

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

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)-; or

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)-; or

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

L is a covalent bond and Y is C_{2-6} alkenyl substituted with oxo, halogen, NO_2, or CN; or

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

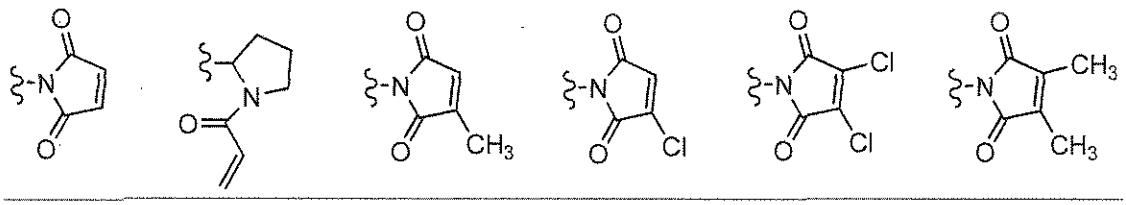
(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

L is –CH_2-, -NH-, -C(O)-, -CH_2NH-, -$NHCH_2$-, –NHC(O)-, -$NHC(O)CH_2OC(O)$-, -$CH_2NHC(O)$-, -$NHSO_2$-, -$NHSO_2CH_2$-, or -SO_2NH-; and Y is selected from:

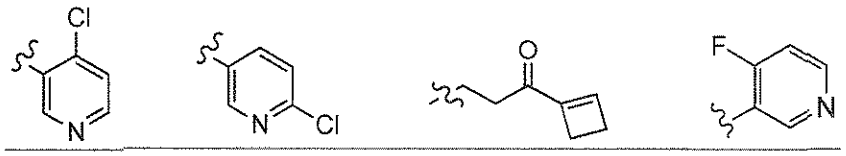
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

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

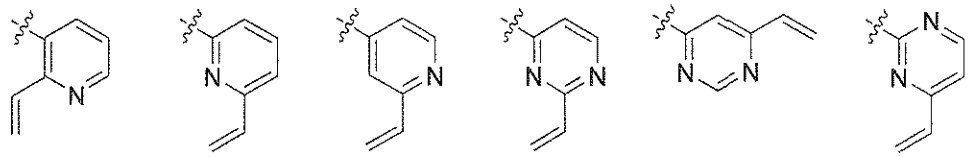
L is a covalent bond, -C(O)-, -N(R)C(O)-, or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and Y is selected from:



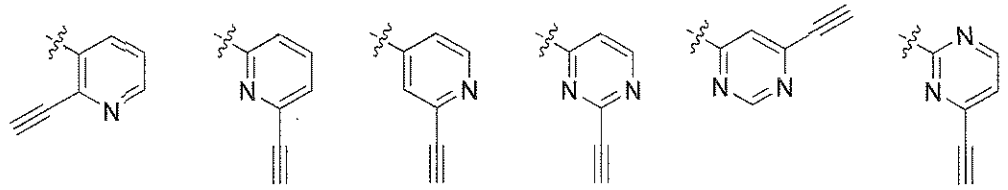
a *b* *c* *d* *e* *f*



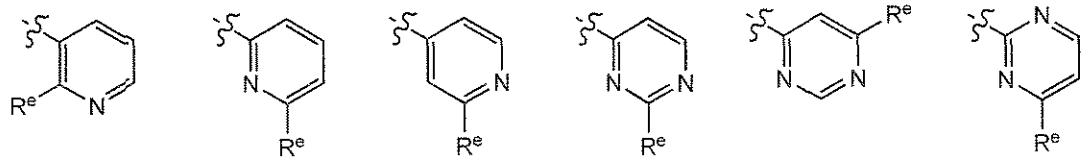
k *l* *r* *x*



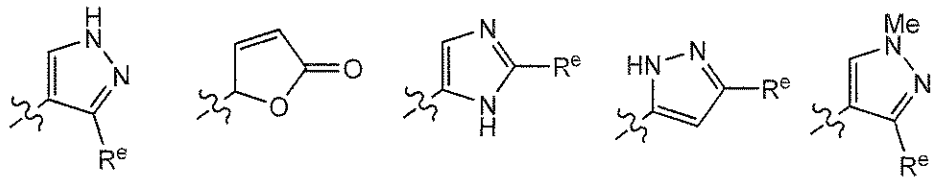
z *aa* *bb* *cc* *dd* *ee*



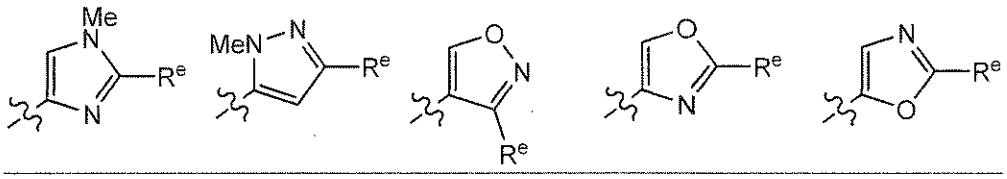
ff *gg* *hh* *ii* *jj* *kk*



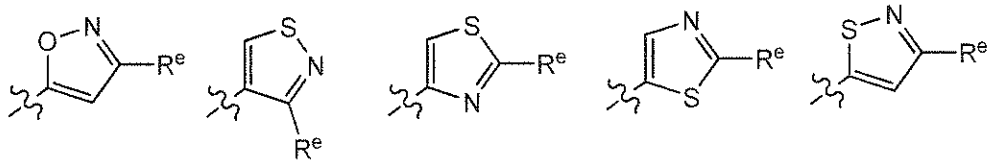
ll *mm* *nn* *oo* *pp* *qq*



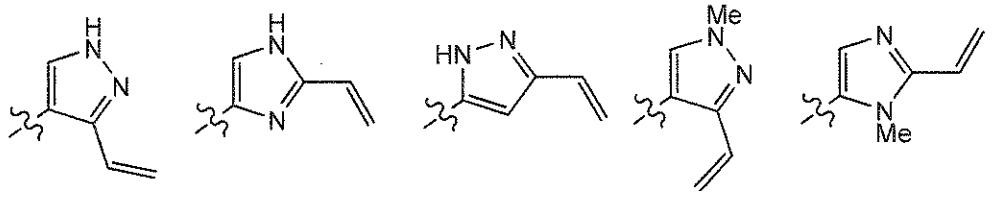
rr *ss* *tt* *uu* *vv*



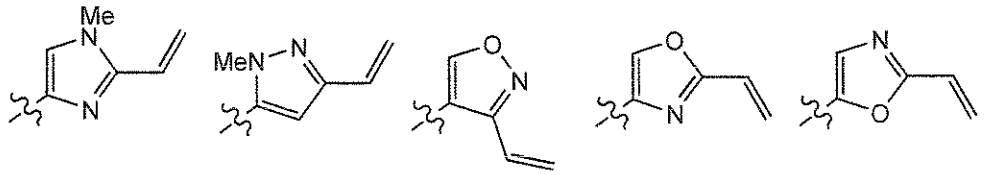
ww *xx* *yy* *zz* *aaa*



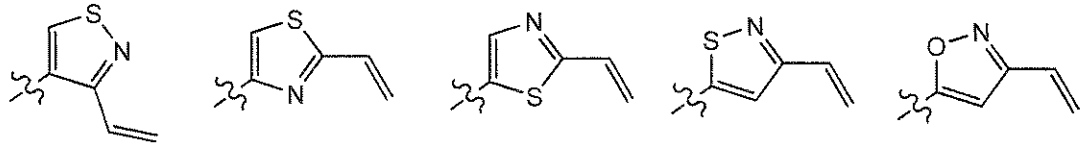
bbb *ccc* *ddd* *eee* *fff*



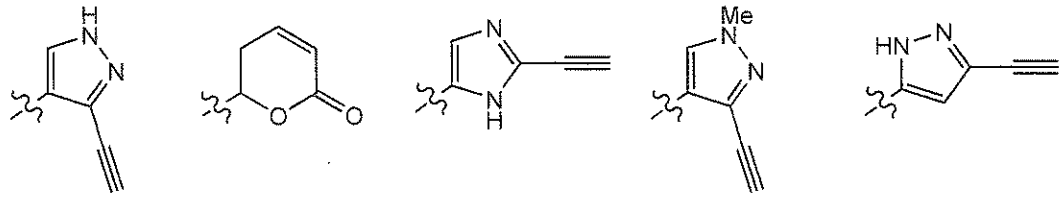
ggg *hhh* *iii* *jjj* *kkk*



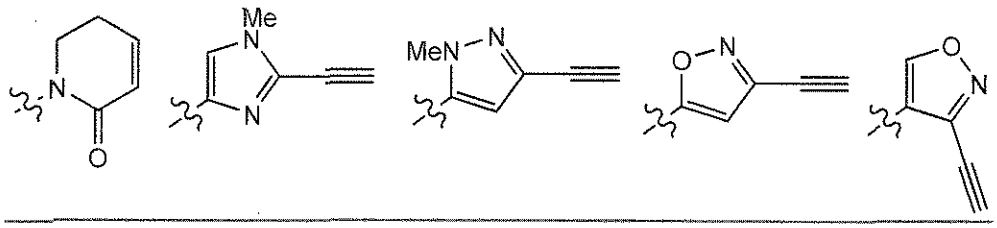
lll *mmm* *nnn* *ooo* *ppp*



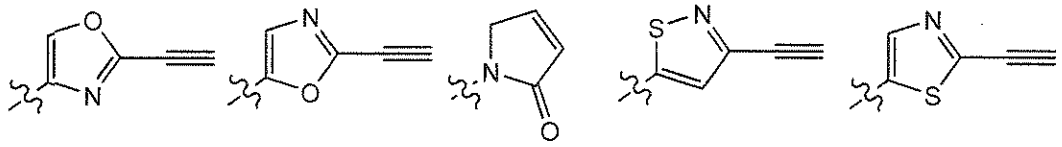
qqq *rrr* *sss* *ttt* *uuu*



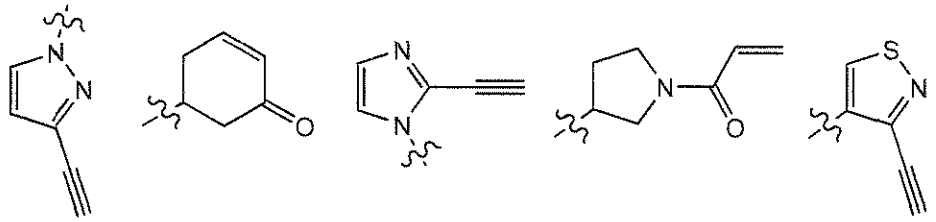
vvv *qqq* *www* *xxx* *yyy*



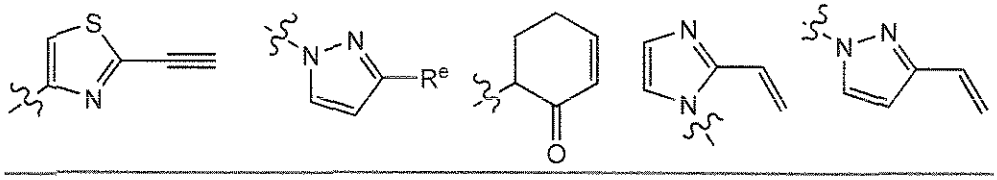
zzz *aaaa* *bbbb* *cccc* *dddd*



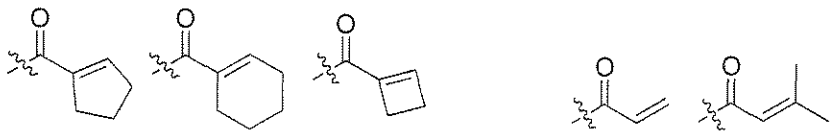
eeee *ffff* *gggg* *hhhh* *iiii*



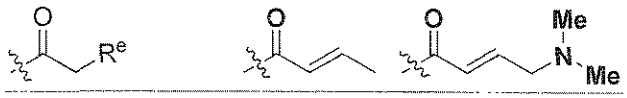
jjjj *kkkk* *llll* *mmmm* *nnnn*



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, C_{1-6} aliphatic substituted with oxo, halogen, NO_2, or CN, or a suitable leaving group selected from alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted

alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, and diazonium, wherein:

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

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

R^y is -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-;

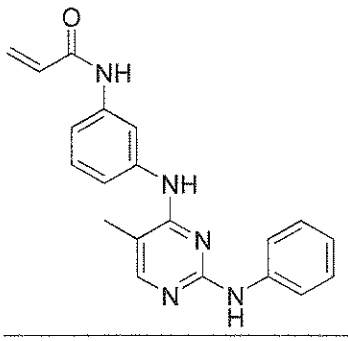
R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R;

m and p are independently 0-4;

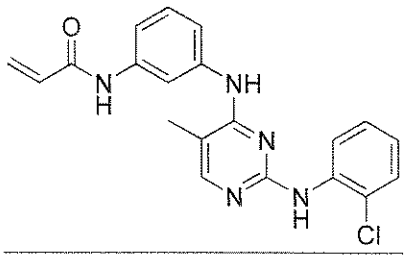
each instance of R^x is independently selected from –R, -OR, -O($CH_2)_q$OR, or halogen, wherein q is 1-4; and

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.

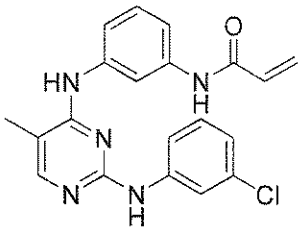
[0006b] In a second aspect of the present disclosure, there is provided a compound selected from the group consisting of:



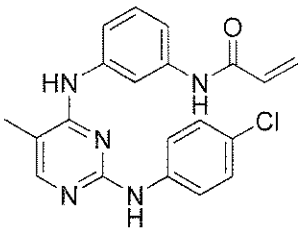
I-7



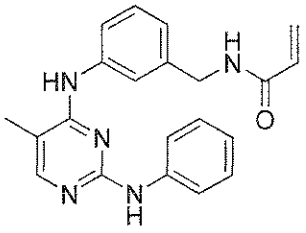
I-13



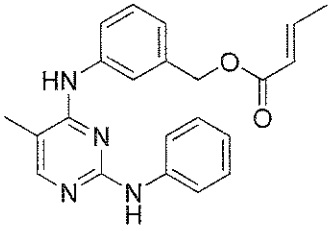
I-14



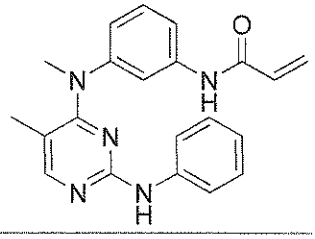
I-15



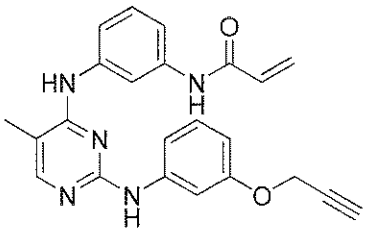
I-24



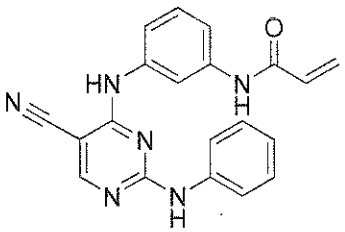
I-25



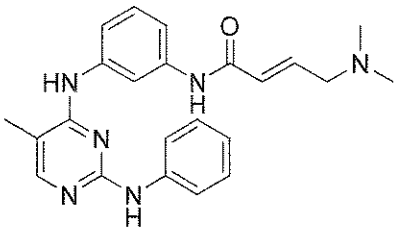
I-34



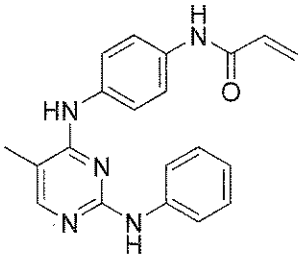
I-35



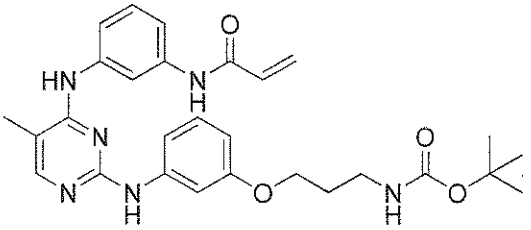
I-36



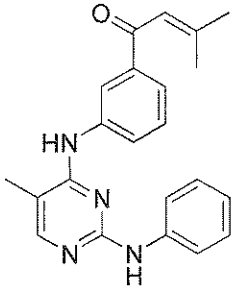
I-38



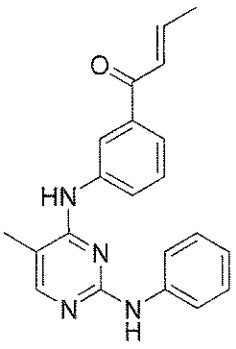
I-39



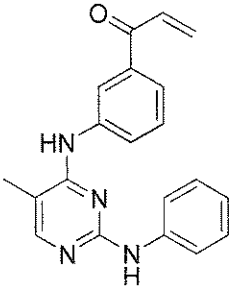
I-45



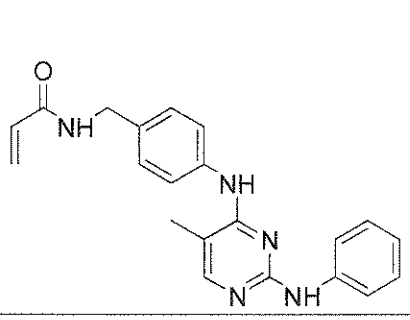
I-47



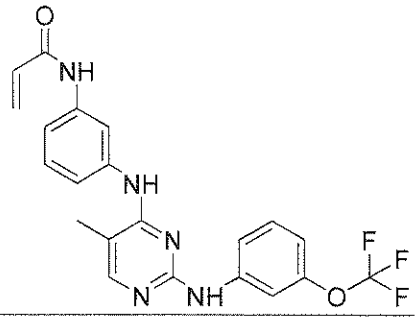
I-48



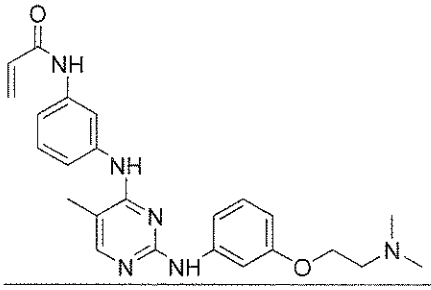
I-49



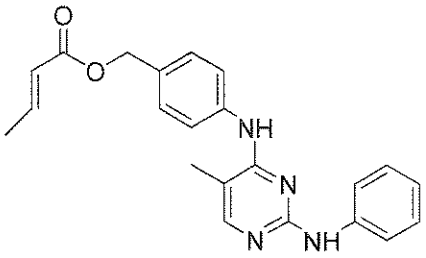
I-57



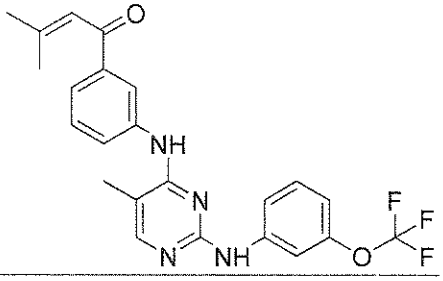
I-58



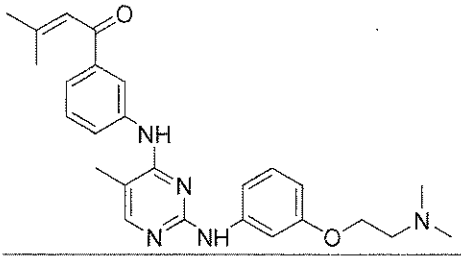
I-59



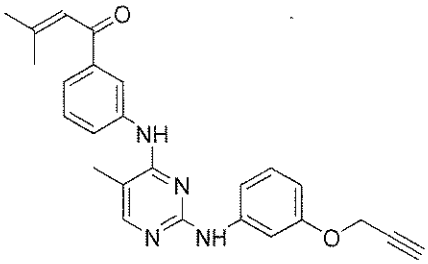
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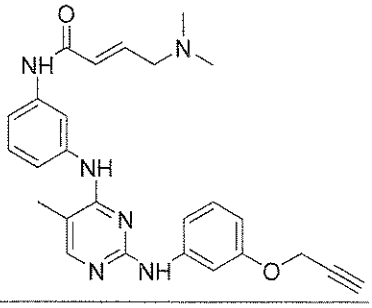
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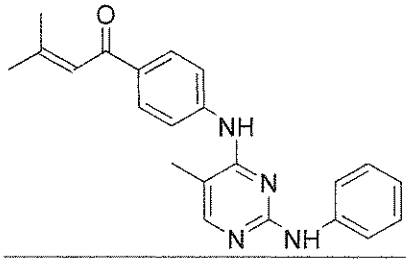
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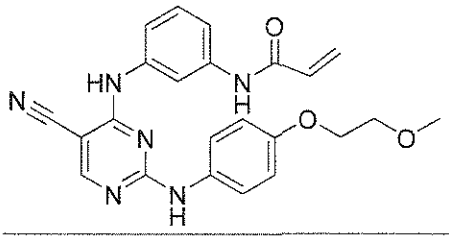
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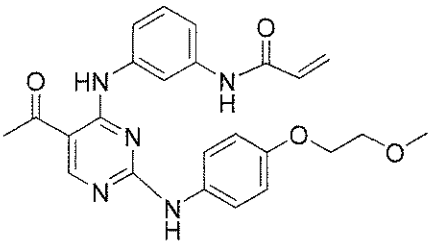
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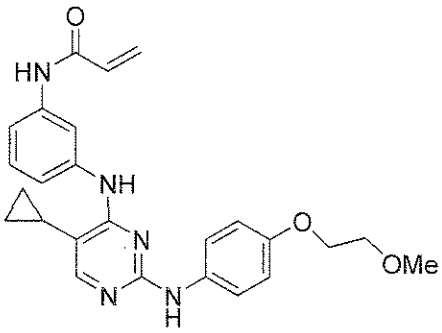
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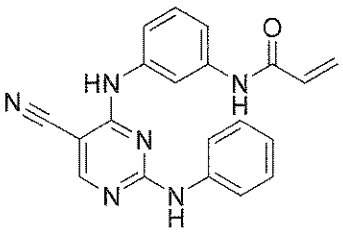
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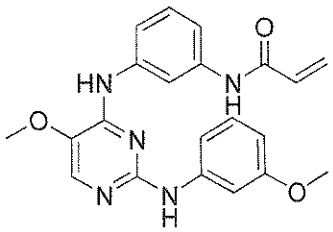
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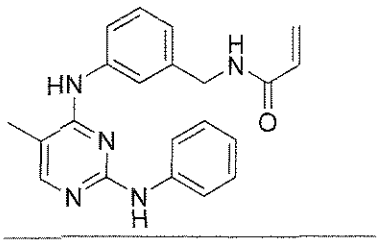
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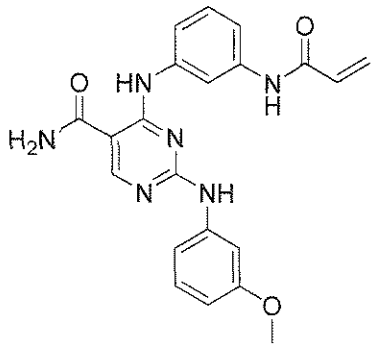
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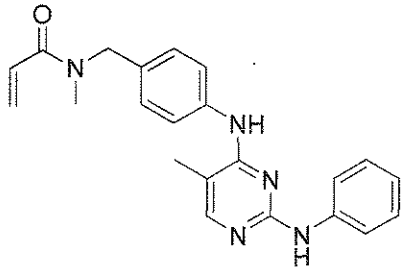
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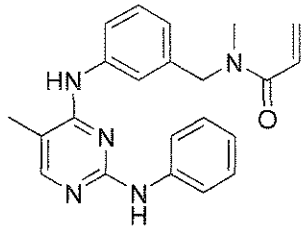
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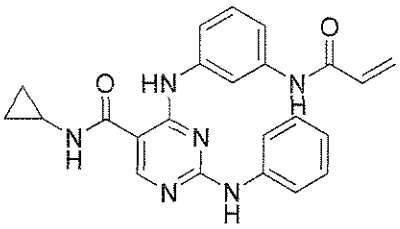
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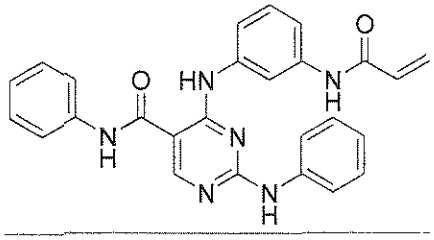
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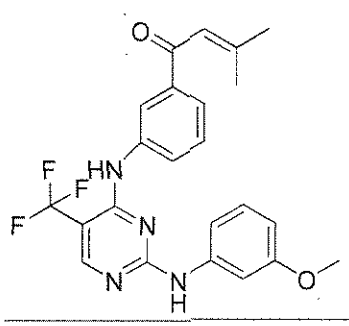
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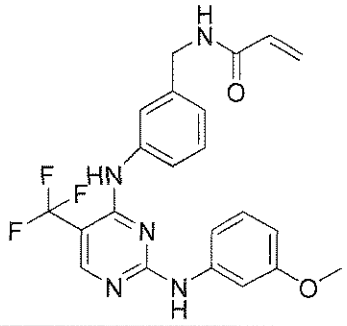
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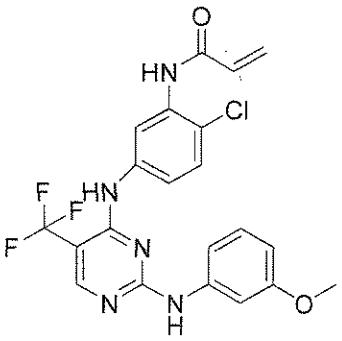
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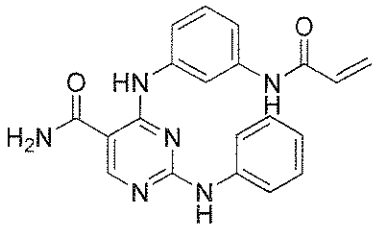
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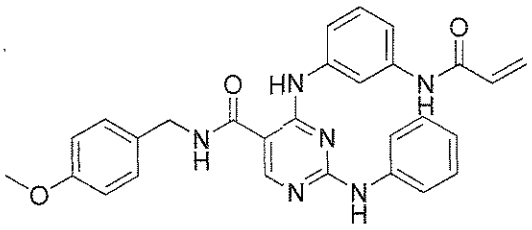
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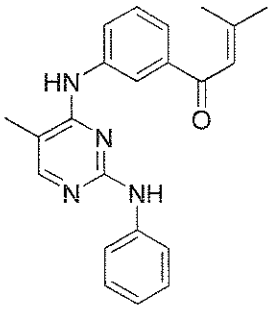
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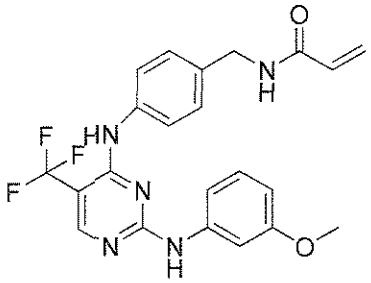
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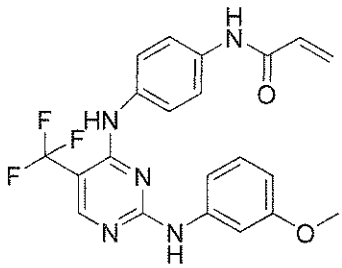
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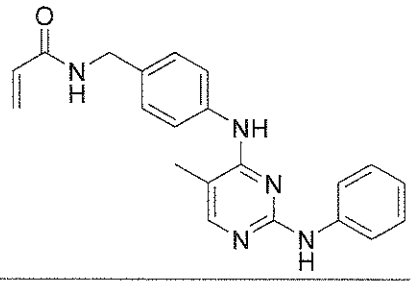
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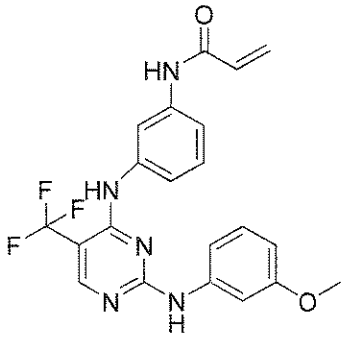
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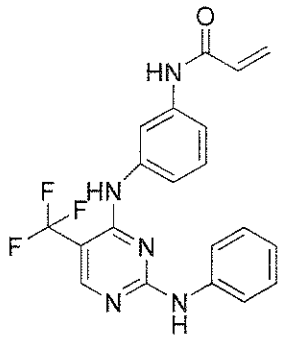
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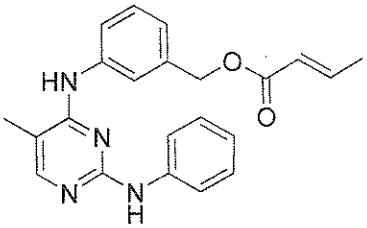
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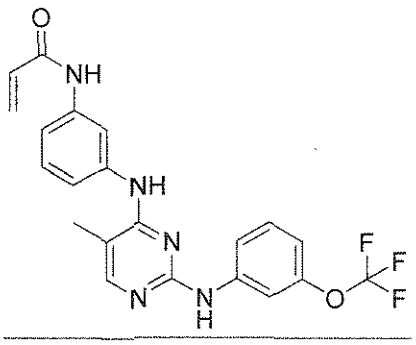
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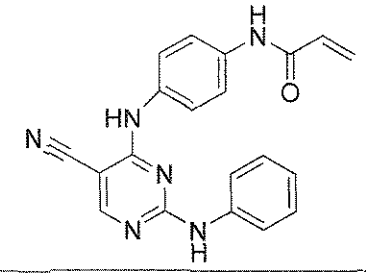
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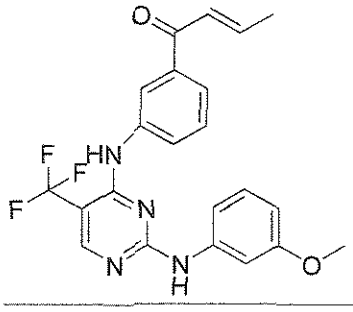
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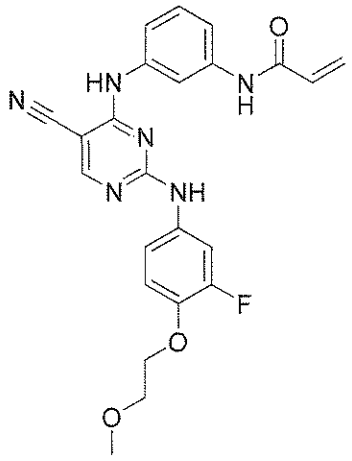
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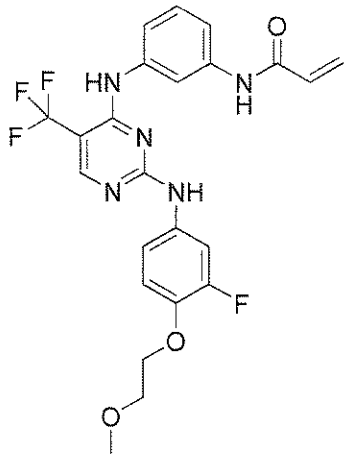
I-253



I-255



I-350



I-352

or a pharmaceutically acceptable salt thereof.

[0006c] In a third aspect of the present disclosure, there is provided a composition comprising a compound as defined herein, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

[0006d] In a fourth aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for the treatment of a BTK-mediated disorder in a patient in need thereof.

[0006e] In a fifth aspect of the present disclosure, there is provided a use of a compound as defined herein for the preparation of a medicament for the treatment of a TEC-kinase-mediated disorder in a patient in need thereof.

[0006f] In a sixth aspect of the present disclosure, there is provided a use of a compound as defined herein for the preparation of a medicament for the treatment of an ErbB1-, ErbB2-, ErbB3-, or ErbB4-mediated disorder in a patient in need thereof.

[0006g] In a seventh aspect of the present disclosure, there is provided a use of a compound as defined herein for the preparation of a medicament for treating a JAK3-mediated disorder in a patient in need thereof.

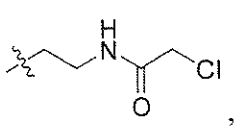
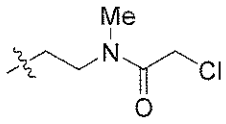
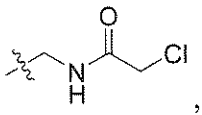
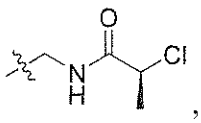
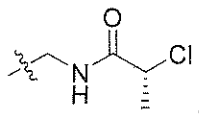
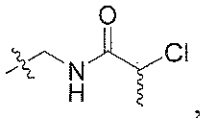
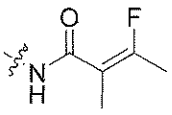
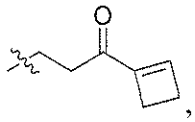
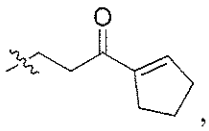
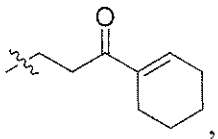
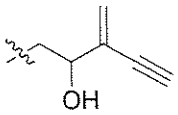
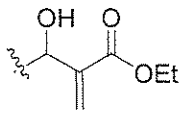
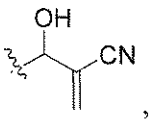
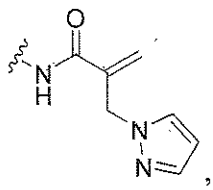
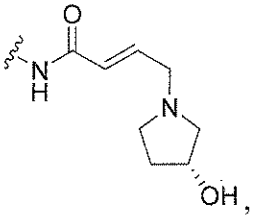
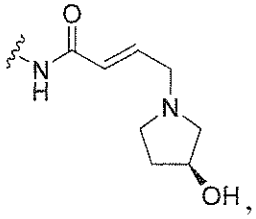
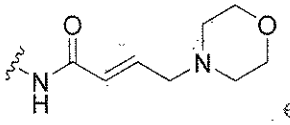
[0007] Compounds of the present ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with abnormal cellular responses triggered by protein kinase-mediated events. Such diseases, disorders, or conditions include those described herein.

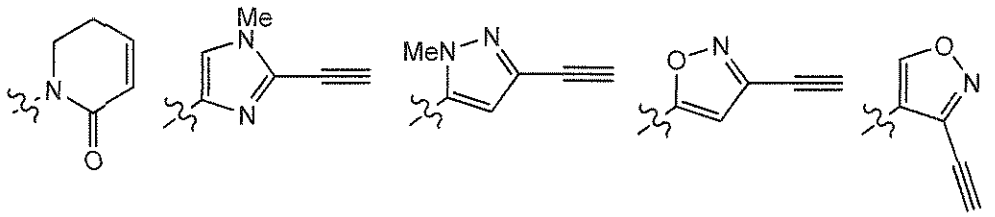
[0008] Compounds provided by the present disclosure~~this invention~~ are also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

BRIEF DESCRIPTION OF THE DRAWINGS

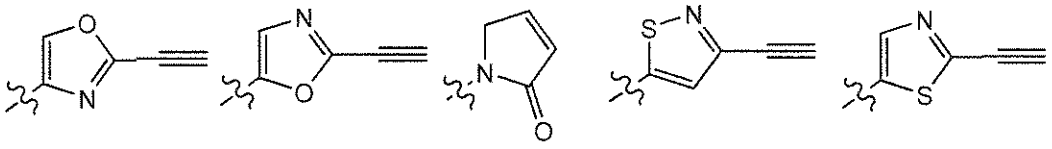
Figure 1 depicts dose-response inhibition of phospho-plc gamma2 (p-plc gamma 2) with compound **I-2** in Ramos Cells; and the results of compound **I-2** in a "washout" experiment.

Figure 2 depicts dose-response inhibition of p-plc gamma2 with compound **I-4** in Ramos Cells; and the results of compound **I-4** in a "washout" experiment.

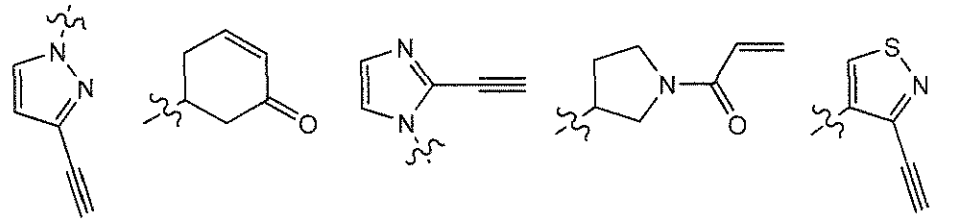
R^1 is a warhead group selected from , , , , , , , , , , , , , , , , , ; or



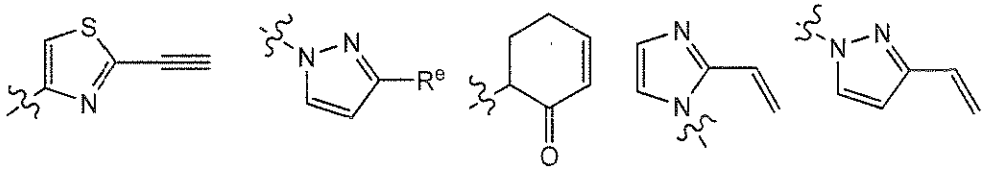
zzz *aaaa* *bbbb* *cccc* *dddd*



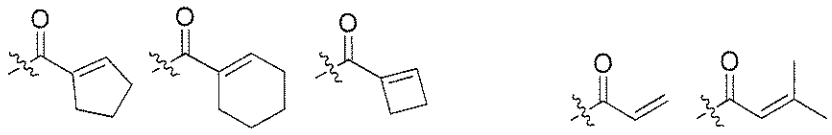
eeee *ffff* *gggg* *hhhh* *iiii*



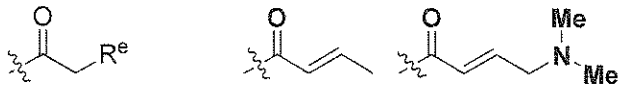
jjjj *kkkk* *llll* *mmmm* *nnnn*



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, C_{1-6} aliphatic substituted with oxo, halogen, NO_2, or CN, or a suitable leaving group selected from alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy,

optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, and 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 -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-;

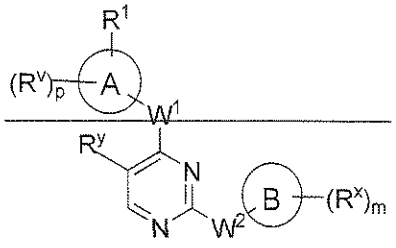
R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R

m and p are independently 0-4;

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.

2. A compound of formula I-b:



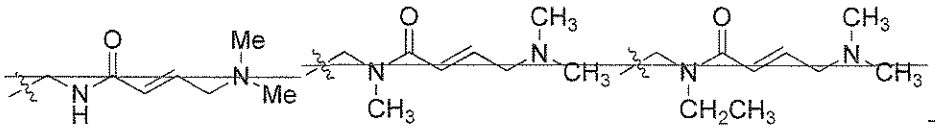
I-b

or a pharmaceutically acceptable salt thereof, wherein:

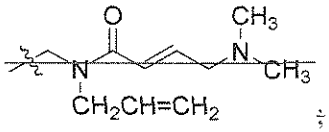
Ring A is optionally substituted phenyl;

Ring B is optionally substituted phenyl;

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



and



;

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

L is $-NRC(O)CH=CH-$, $-NRC(O)CH=CHCH_2N(CH_3)-$, $-NRC(O)CH=CHCH_2O-$, $-NRSO_2CH=CH-$, $-NRSO_2CH=CHCH_2-$, $-NRC(O)(C=N_2)-$, $-NRC(O)(C=N_2)C(O)-$, $-NRC(O)C(=CH_2)CH_2-$, $-CH_2NRC(O)-$, $-CH_2NRC(O)CH=CH-$, $-CH_2CH_2NRC(O)-$, $-CH_2NRC(O)$cyclopropylene-, $-C(O)CH=C(CH_3)-$, $-C(O)CH=CHCH_2NH(CH_3)-$, $-C(O)CH=CH-$, $-CH_2C(O)CH=CH-$, $-CH_2C(O)CH=C(CH_3)-$, $-CH_2CH_2C(O)CH=CH-$, $-CH_2CH_2C(O)CH=CHCH_2-$, $-CH_2CH_2C(O)CH=CHCH_2N(CH_3)-$, $-CH_2CH_2C(O)CH=C(CH_3)-$, $-CH(CH_3)OC(O)CH=CH-$, $-CH_2OC(O)CH=CHCH_2-$, $-CH_2OC(O)CH=CH-$ 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;

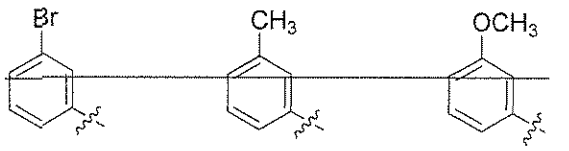
R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or C(O)R;

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

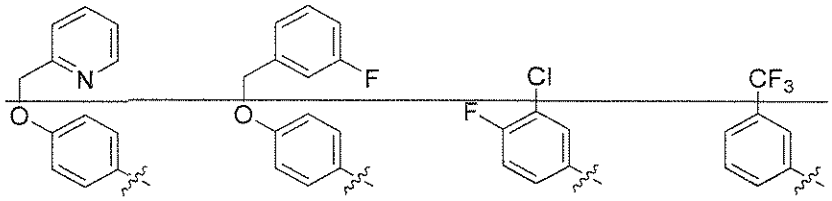
R^x is selected from -R, halogen, -OR, $-O(CH_2)_qCO_2R$, $-NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1, 2, 3 or 4; and

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.

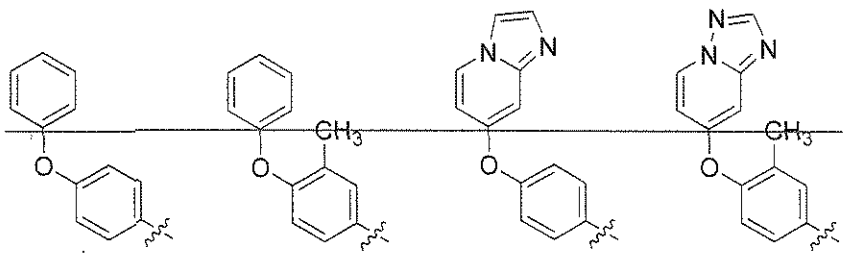
3. The compound according to claim 1 or claim 2, wherein Ring A is selected from:



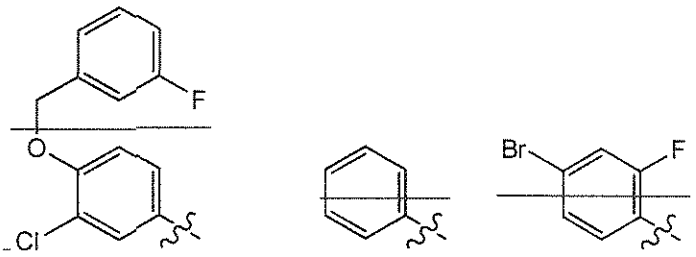
i *ii* *iii*



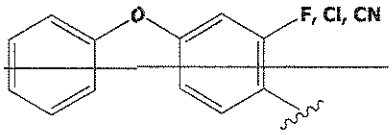
v *vi* *vii* *viii*



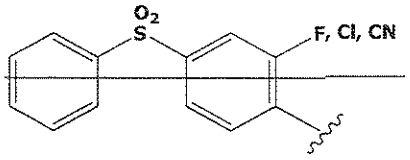
ix *x* *xi* *xii*



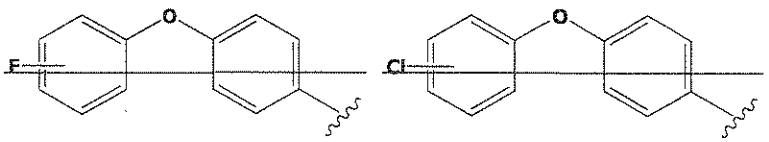
xiv *xvi* *xvii*



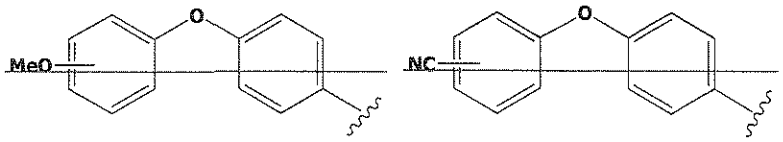
xviii



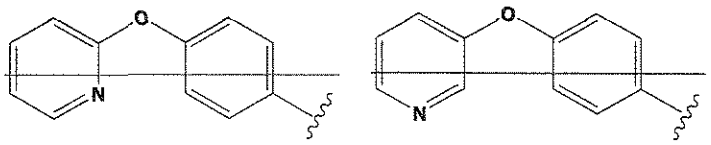
xix



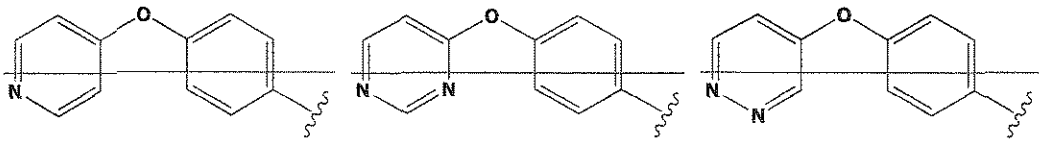
~~xxvii~~ ~~xxviii~~



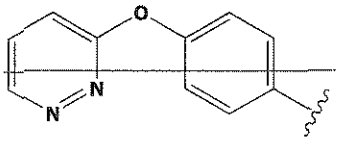
~~xxix~~ ~~xxx~~



~~xxxv~~ ~~xxxvi~~

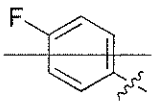


~~xxxvii~~ ~~xxxviii~~ ~~xxxix~~

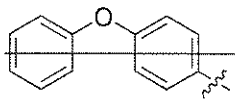


~~xl~~

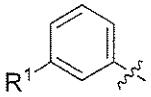
2. The compound according to claim 1, wherein Ring A is selected from:



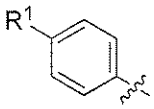
~~*lvi*~~



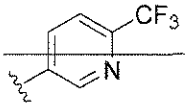
~~*lxv*~~



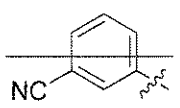
lxiii



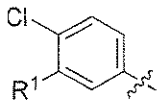
lxvi



~~*lxvii*~~

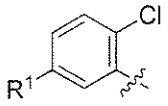


~~*lxx*~~



lxxi

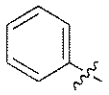
~~or~~



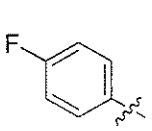
lxxxi.

~~4~~ 3. The compound according to claim ~~3~~2, wherein Ring A is selected from ~~*i, ii, v, vi, vii, ix, xiv, xvi,*~~ *lxiii*, *lxxi*, and *lxxxi*.

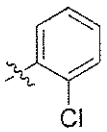
~~5~~4. The compound according to claim 1 ~~or claim 2~~, wherein Ring B is selected from:



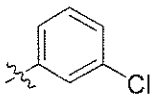
xi



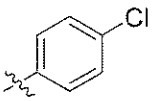
xv



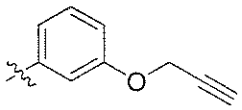
xviii



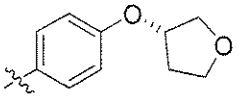
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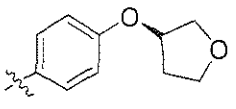
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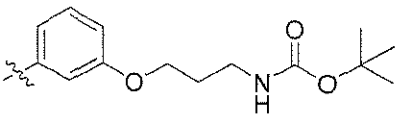
xxiii



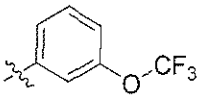
xxv



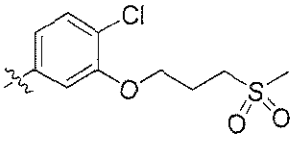
xxvi



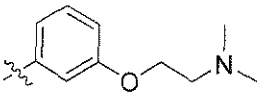
xxvii



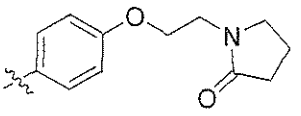
xxix



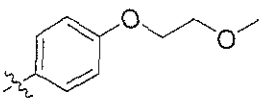
xxx



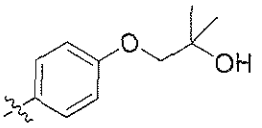
xxxi



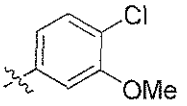
xxxiii



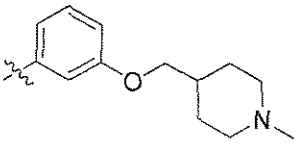
xxxiv



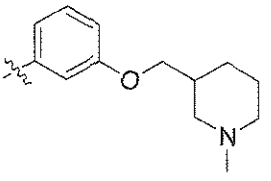
xxxv



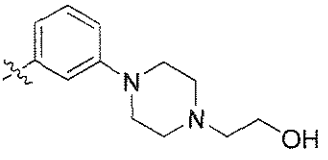
xxxvii



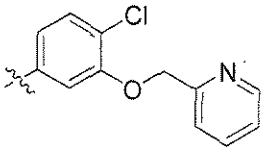
xxxix



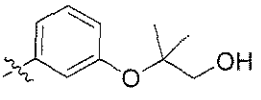
xl



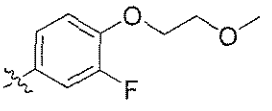
xliv



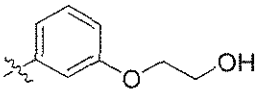
xlv



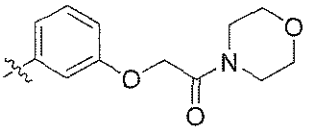
xlvi



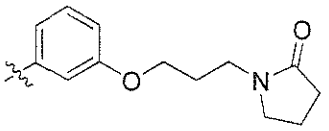
xlviii



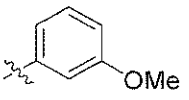
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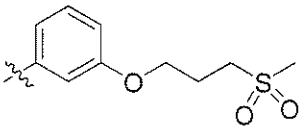
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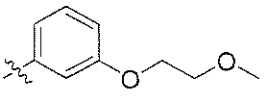
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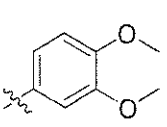
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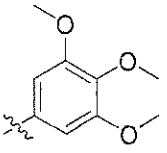
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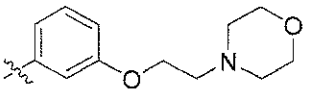
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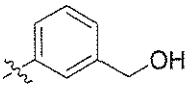
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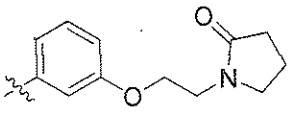
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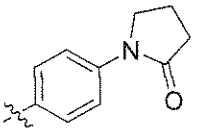
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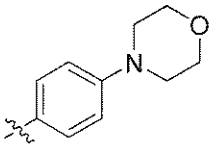
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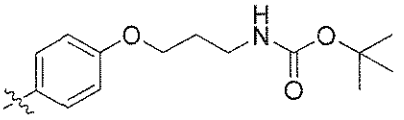
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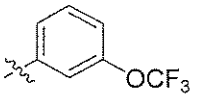
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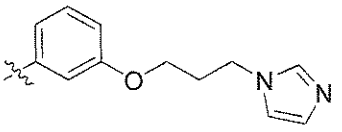
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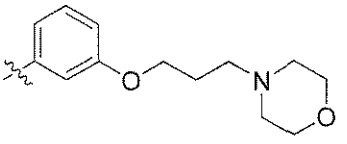
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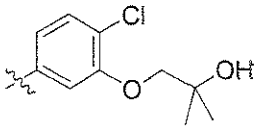
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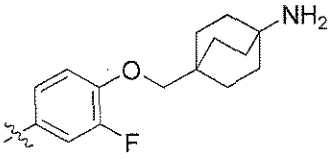
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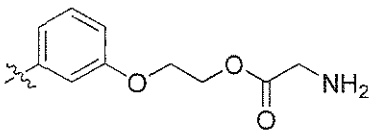
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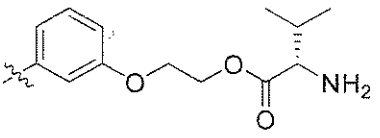
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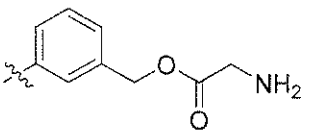
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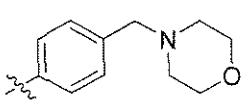
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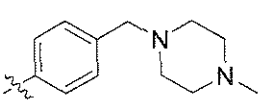
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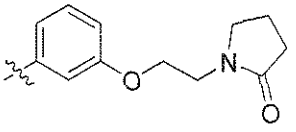
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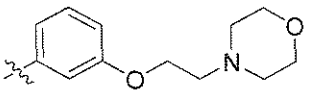
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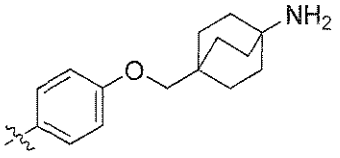
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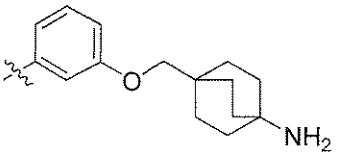
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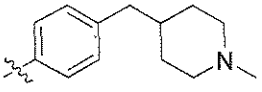
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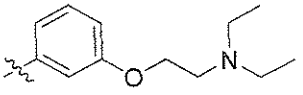
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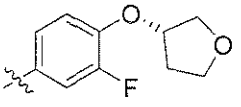
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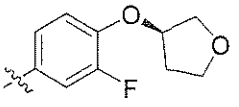
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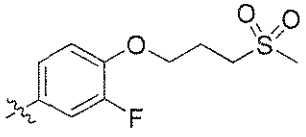
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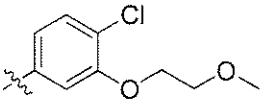
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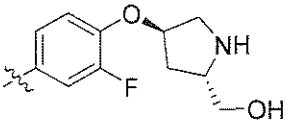
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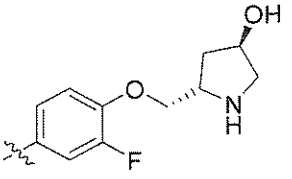
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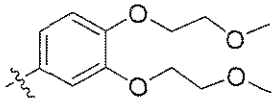
cv



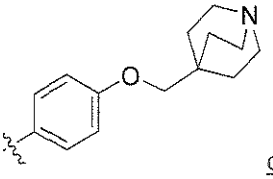
or



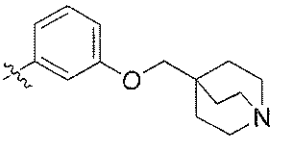
cvi *cvii*



cviii



or



cix *cx.*

65. The compound according to claim ~~5~~4, wherein Ring B is selected from ***xi***, ***xvii***, ***xix***, ***xx***, ***xxv***, ***xxvi***, ***xxxiv***, ***xxxv***, ***xlvi***, ***xlviii***, ***l***, ***lviii***, ***lxiv***, ***lxxviii***, ***lxxxiii***, ***xciv***, ***cii***, ***ciii***, ***civ***, and ***cv***.

~~7~~6. The compound according to claim 1, wherein:

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

~~8~~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 at least one methylene unit of ~~-~~L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one additional methylene units of L is optionally 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.

~~9~~8. The compound according to claim ~~8~~7, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

~~10~~9. The compound according to claim ~~8~~7, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -OC(O)-.

~~11~~10. The compound according to claim ~~8~~7, 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$_2$-, or -NRC(O)C(=CH$_2$)CH$_2$; wherein the R group of L 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.

~~12~~11. The compound according to claim ~~11~~10, 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$_2$-, or -NHC(O)C(=CH$_2$)CH$_2$.

~~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.~~

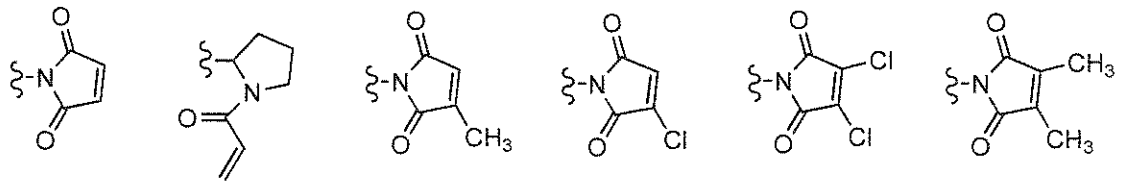
~~14. The compound according to claim 13, wherein L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH$_2$N(CH$_3$)-, -NHC(O)CH=CHCH$_2$O-, -CH$_2$NHC(O)CH=CH-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH$_2$-, -NHC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NHC(O)-, -CH$_2$CH$_2$NHC(O)-, or -CH$_2$NHC(O)cyclopropylene-.~~

~~15~~12. 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)-.

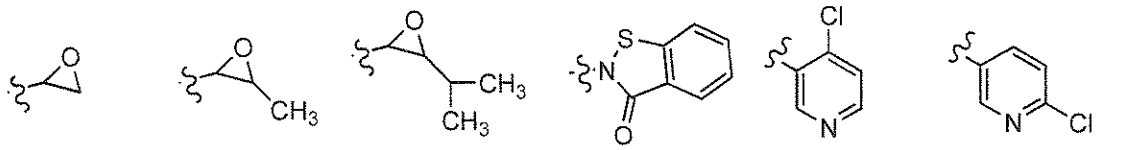
~~16~~13. The compound according to claim 1, wherein L is a covalent bond, –CH_2-, -NH-, -C(O)-, -CH_2NH-, -$NHCH_2$-, –NHC(O)-, -NHC(O)CH_2OC(O)-, -CH_2NHC(O)-, -$NHSO_2$-, -$NHSO_2CH_2$-, or -SO_2NH-.

~~17~~14. The compound according to claim ~~16~~13, wherein L is a covalent bond.

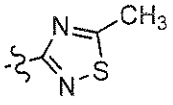
~~18~~15. The compound according to claim ~~16~~-13 or ~~17~~14, wherein Y is selected from:



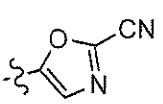
a *b* *c* *d* *e* *f*



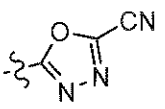
g *h* *i* *j* *k* *l*



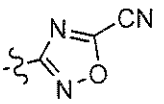
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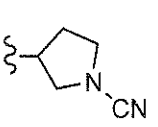
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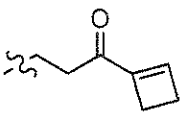
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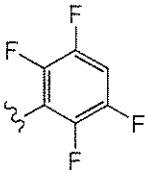
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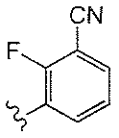
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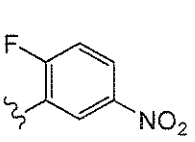
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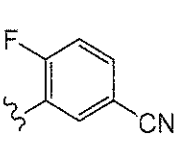
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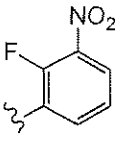
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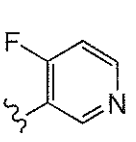
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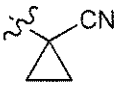
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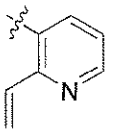
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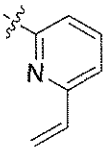
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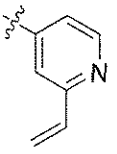
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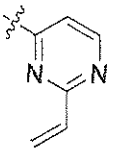
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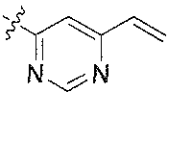
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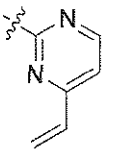
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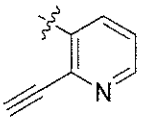
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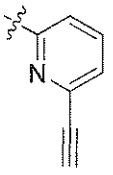
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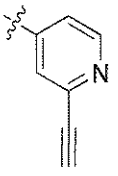
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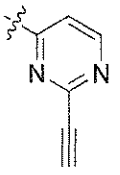
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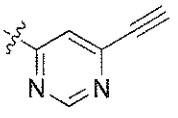
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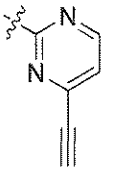
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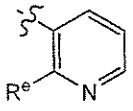
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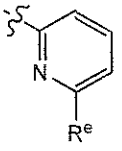
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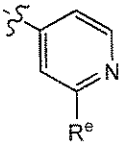
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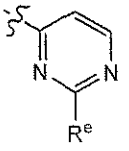
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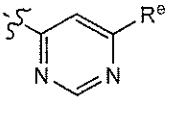
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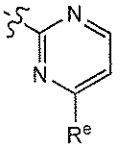
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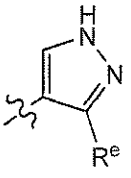
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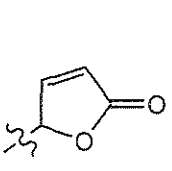
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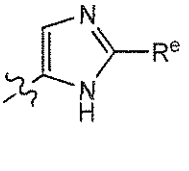
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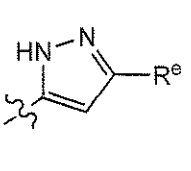
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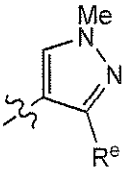
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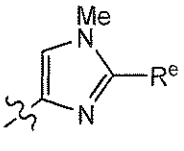
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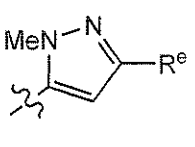
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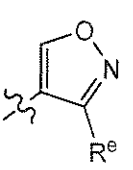
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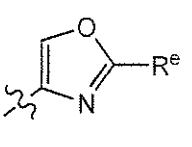
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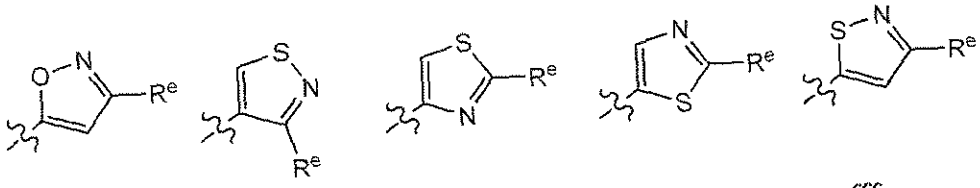


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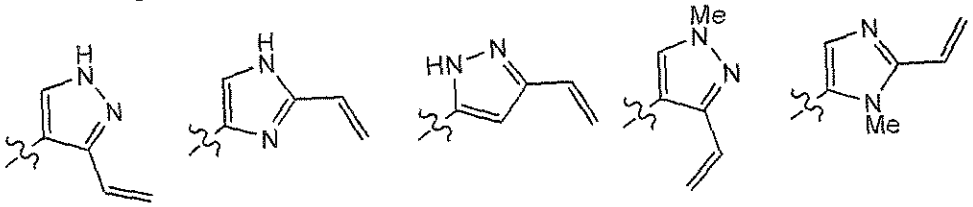


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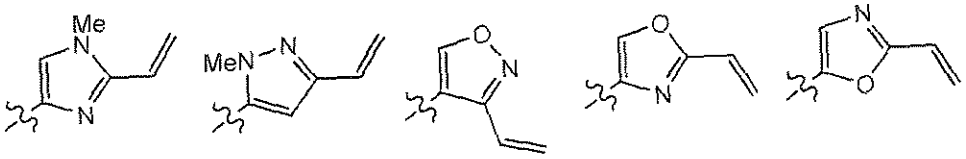
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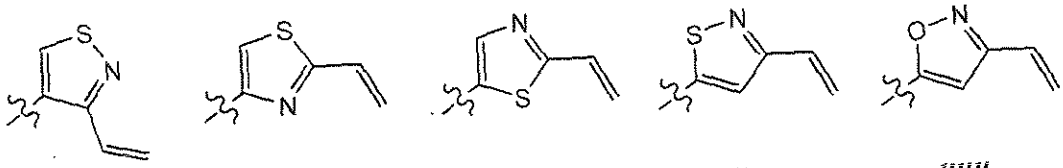
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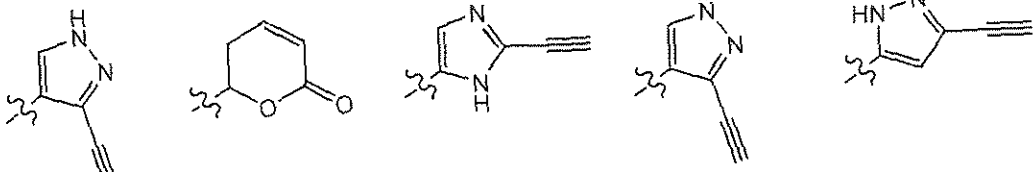
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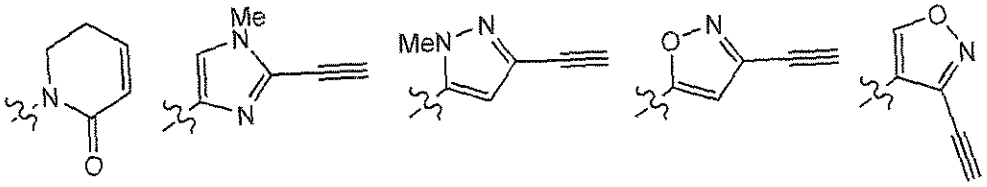
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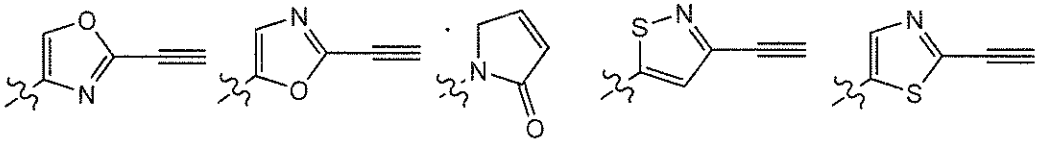
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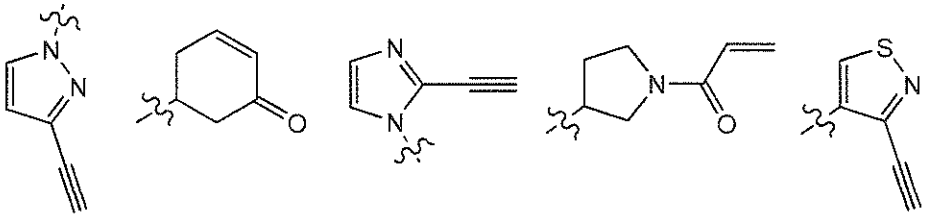
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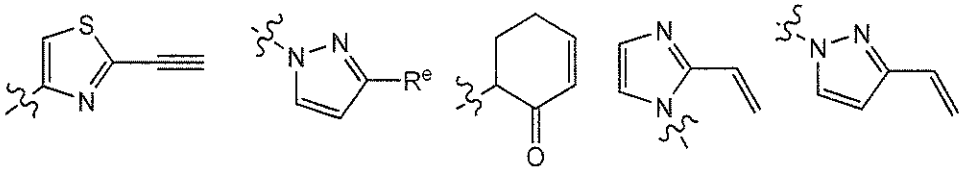
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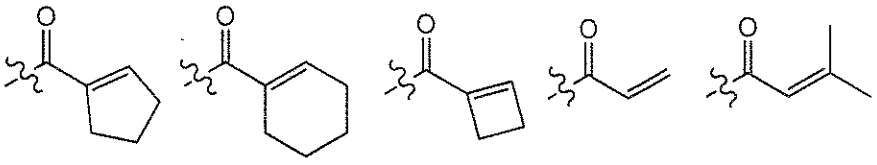
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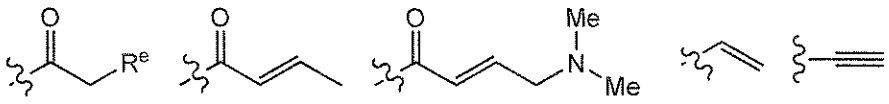
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oooo *pppp* *qqqq* *rrrr* *ssss*



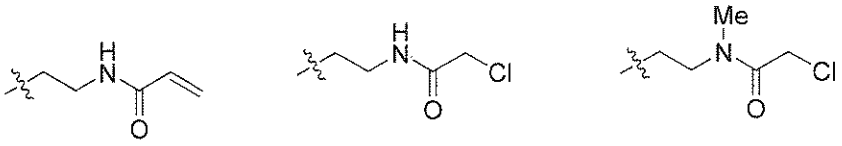
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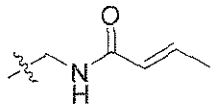
yyyy *zzzz* *aaaaa* *bbbbb* *ccccc*

wherein each R^e is independently selected from halogen.

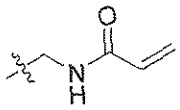
~~19~~16. The compound according to claim 1, wherein R^1 is selected from:



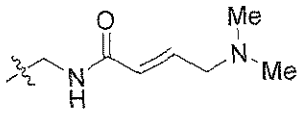
b *c* *d*



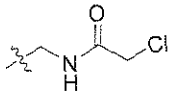
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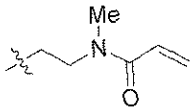
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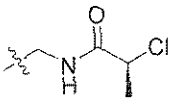
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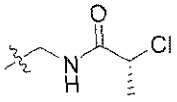
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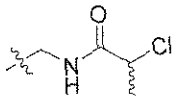
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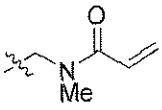
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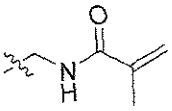
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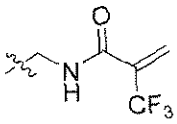
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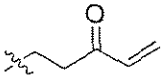
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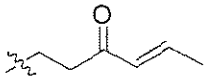
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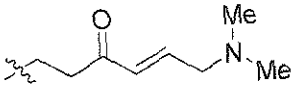
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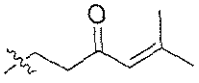
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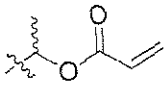
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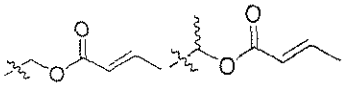
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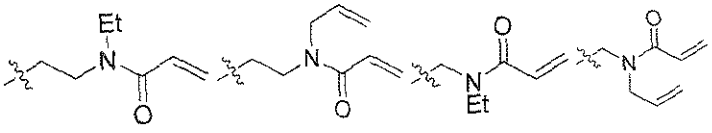
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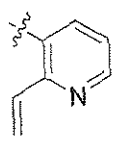
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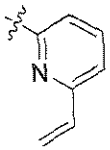
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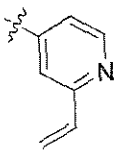
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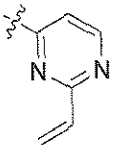
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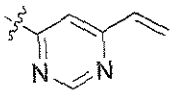
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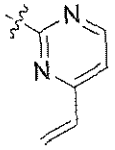
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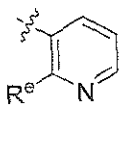
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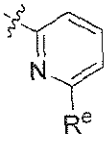
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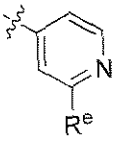
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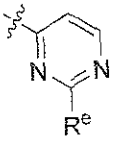
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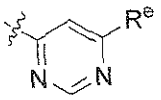
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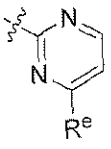
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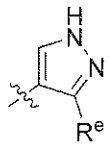
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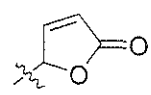
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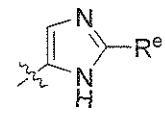
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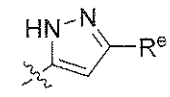
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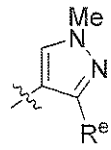
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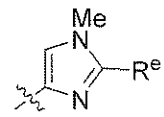
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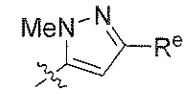
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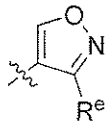
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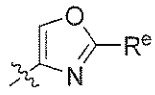
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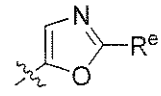
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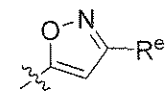
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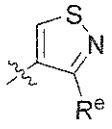
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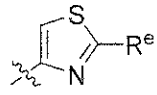
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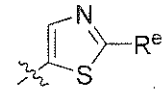
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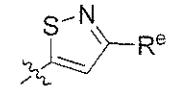
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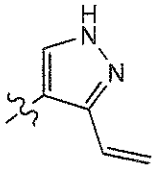
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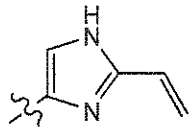
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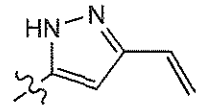
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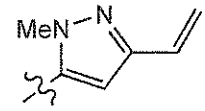
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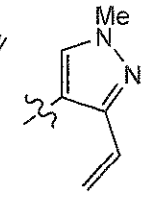
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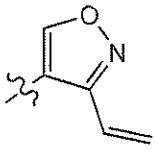


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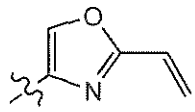


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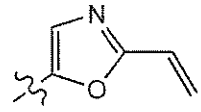




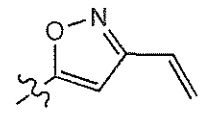
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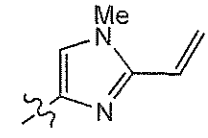
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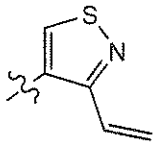
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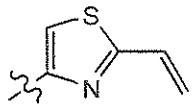
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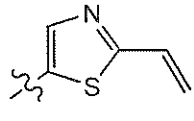
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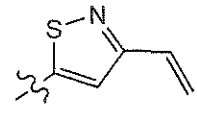
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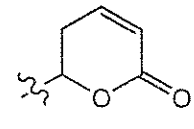
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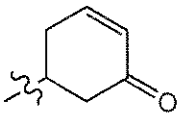
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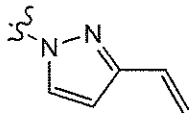
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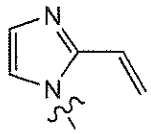
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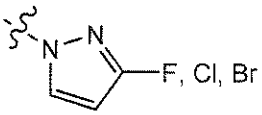
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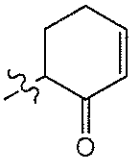
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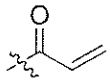
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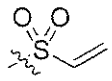
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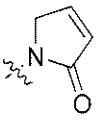
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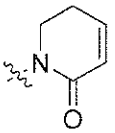
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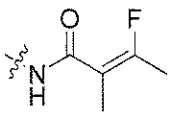
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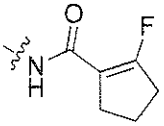
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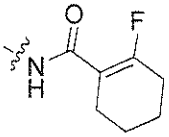
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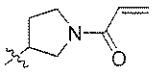
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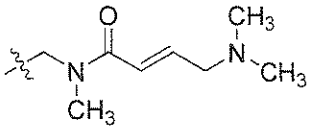
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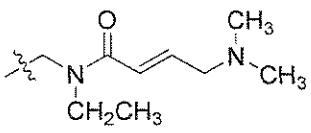
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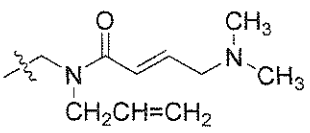
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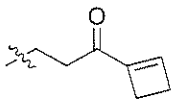
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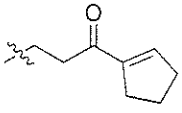
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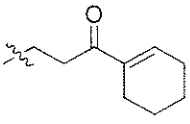
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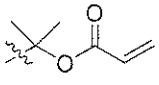
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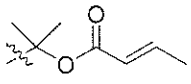
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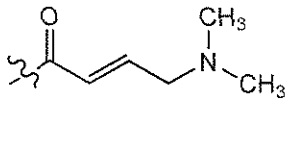
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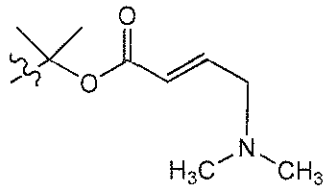
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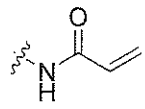
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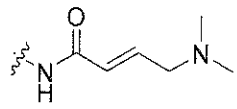
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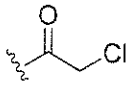
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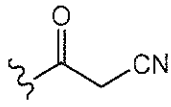
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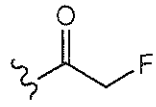
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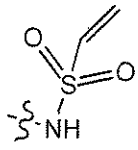
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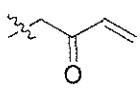
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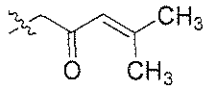
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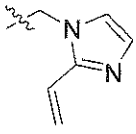
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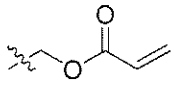
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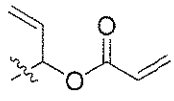
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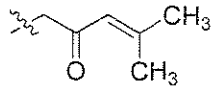
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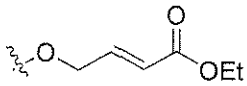
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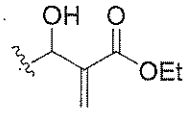
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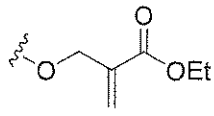
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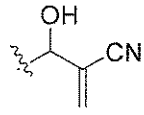
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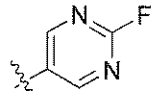
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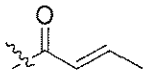
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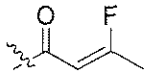
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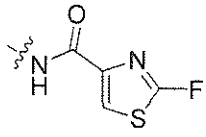
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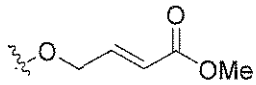
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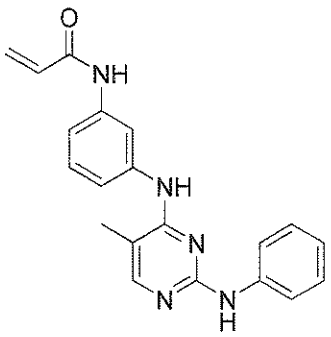
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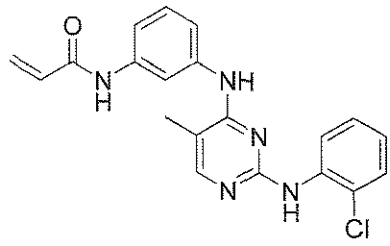
wwwwww or *xxxxxx*

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

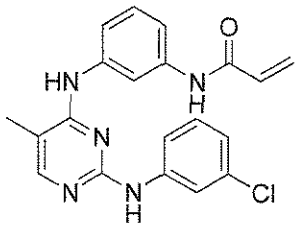
~~20~~17. A compound selected from the group consisting of:



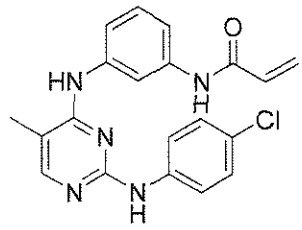
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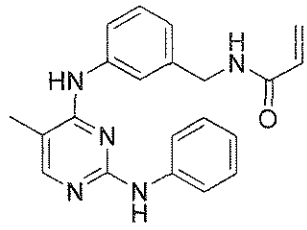
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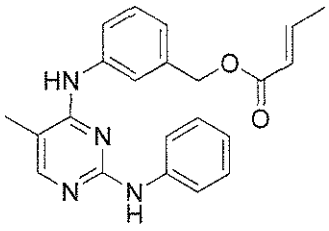
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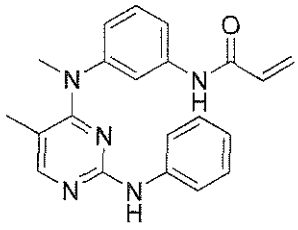
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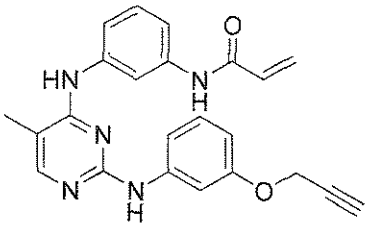
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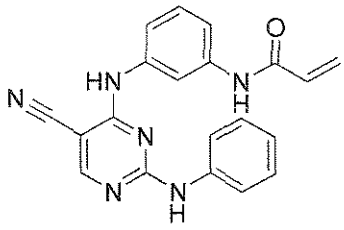
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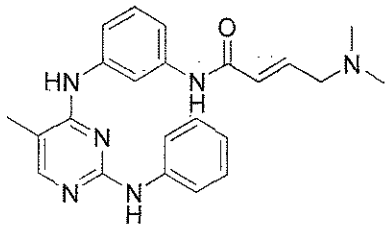
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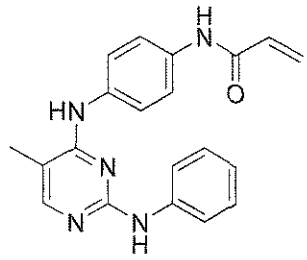
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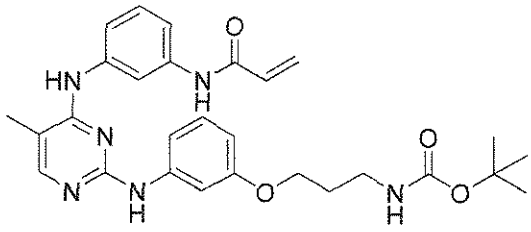
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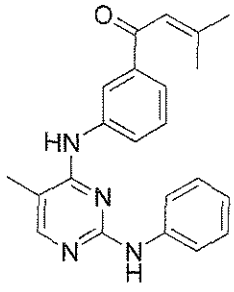
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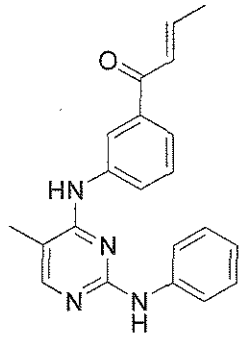
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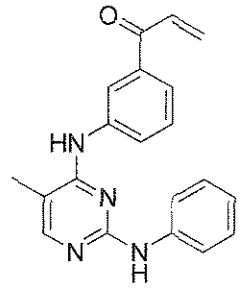
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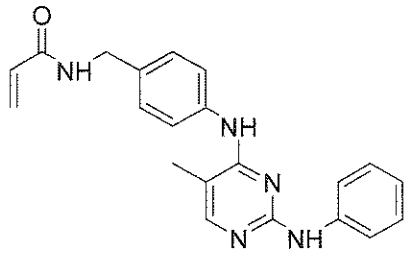
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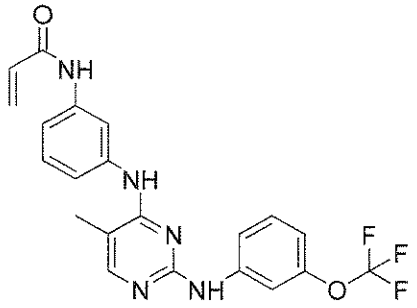
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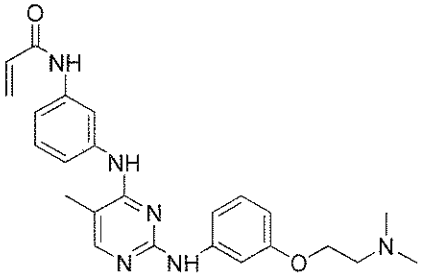
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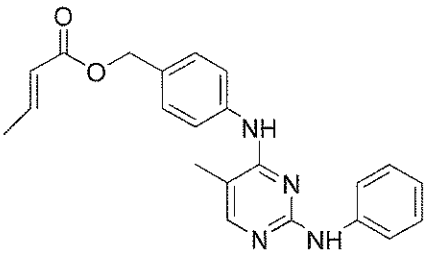
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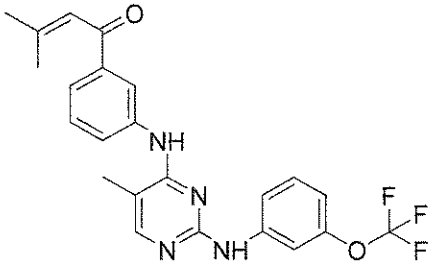
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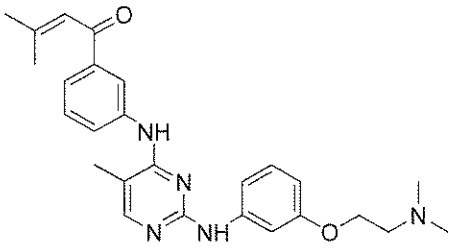
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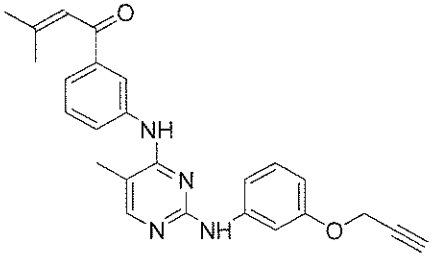
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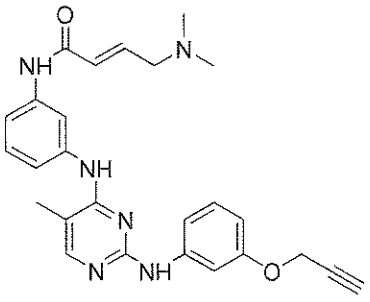
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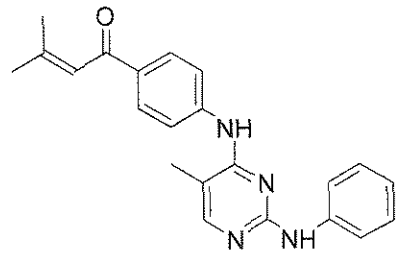
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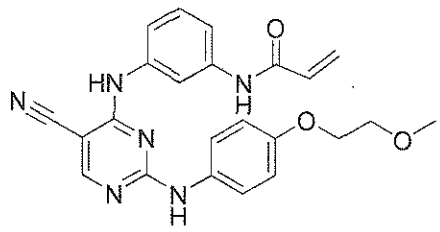
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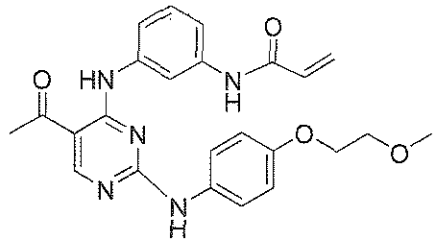
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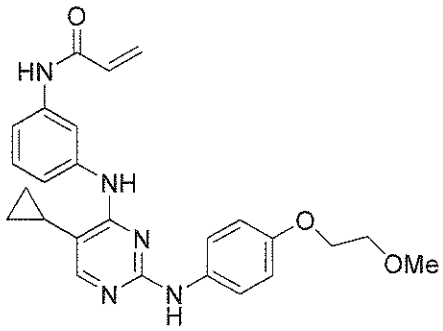
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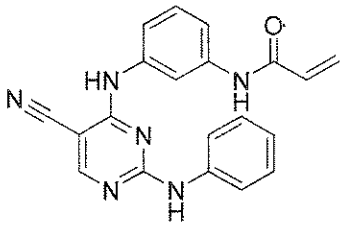
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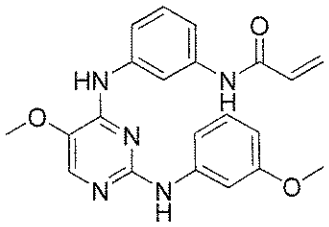
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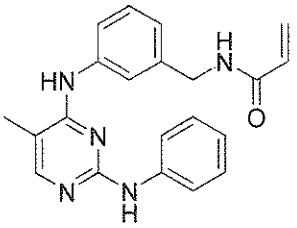
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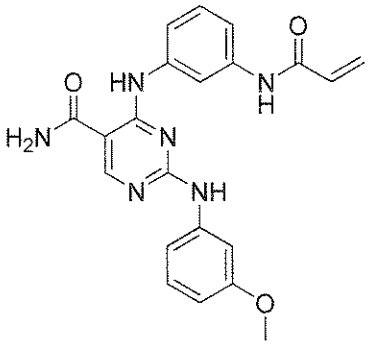
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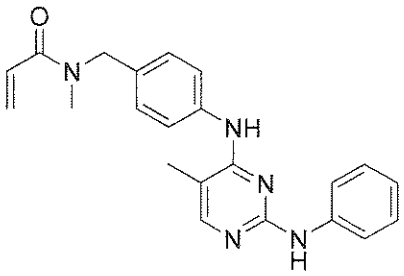
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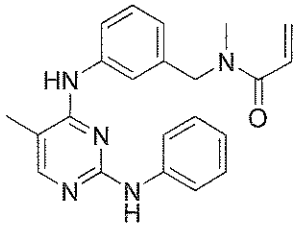
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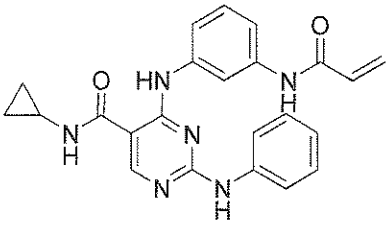
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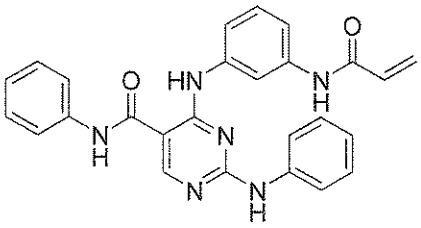
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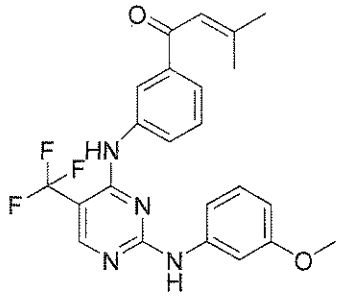
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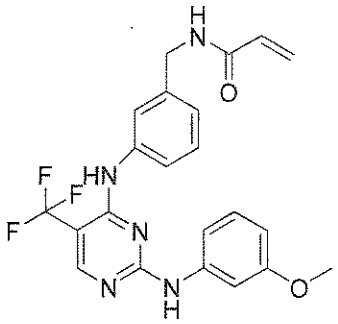
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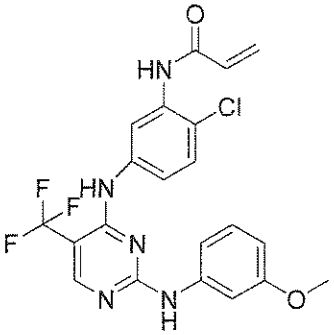
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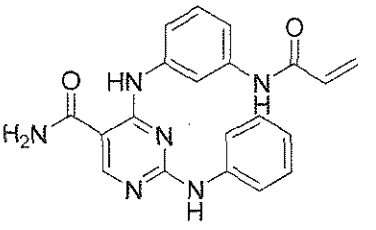
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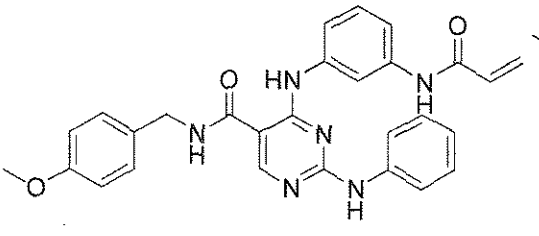
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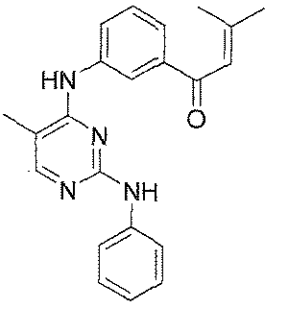
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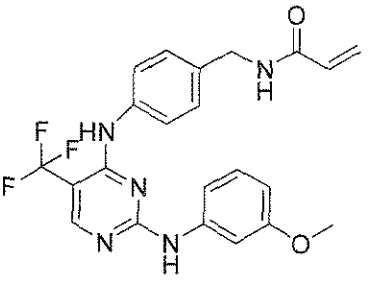
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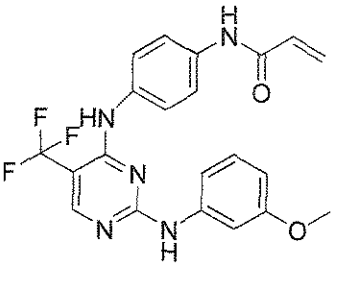
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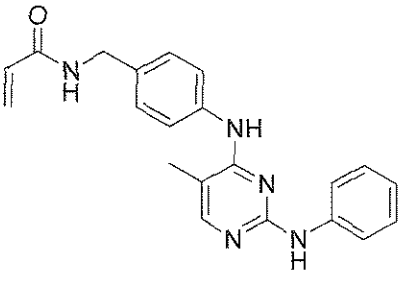
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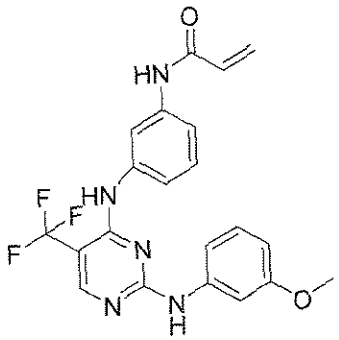
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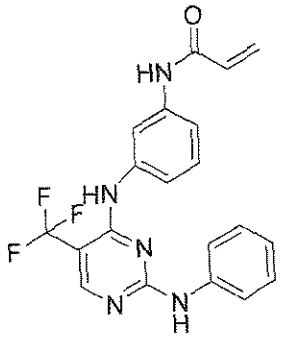
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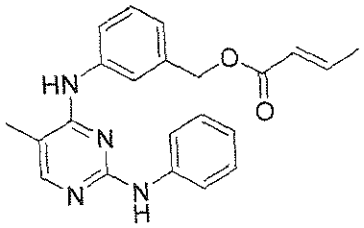
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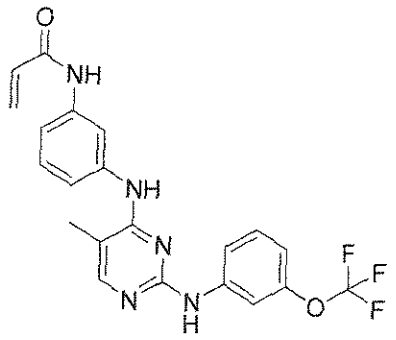
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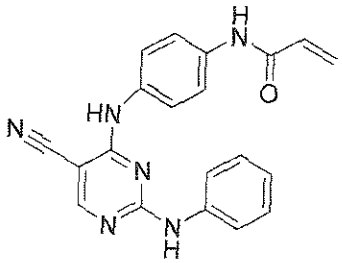
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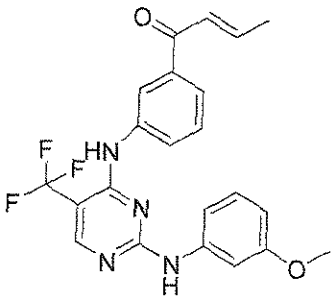
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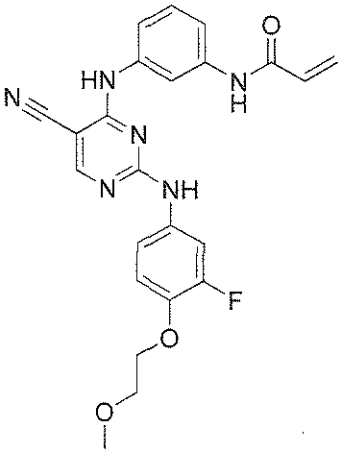
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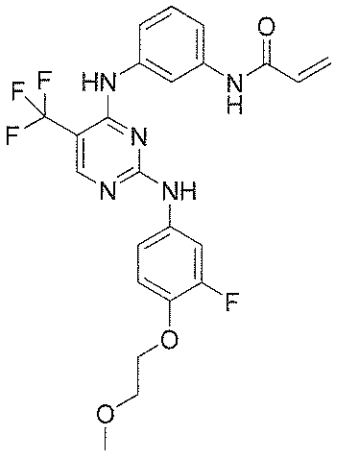
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I-255



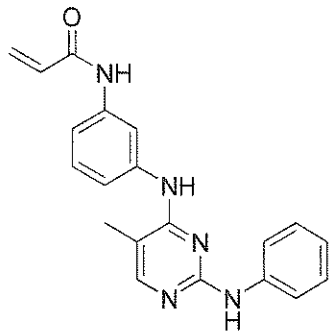
I-350



I-352

or a pharmaceutically acceptable salt thereof.

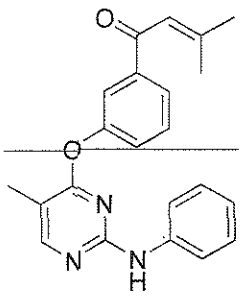
~~21~~18. The compound according to claim ~~20~~17 having the structure:



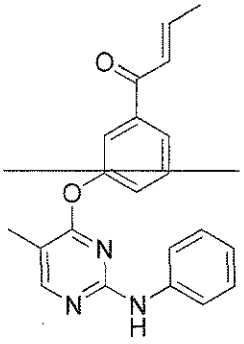
I-7

or a pharmaceutically acceptable salt thereof.

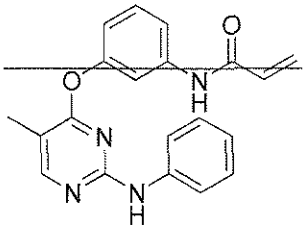
~~22. The compound according to claim 2 selected from the group consisting of:~~



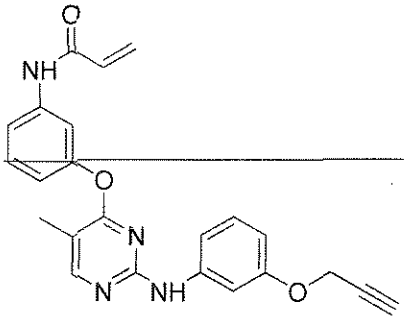
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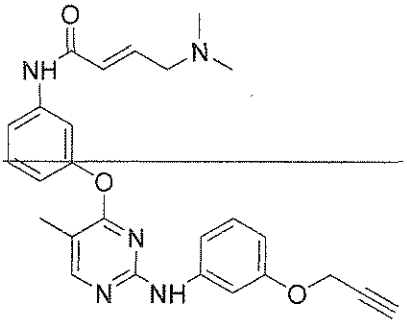
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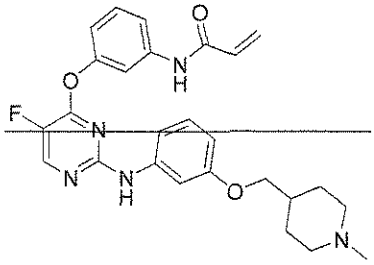
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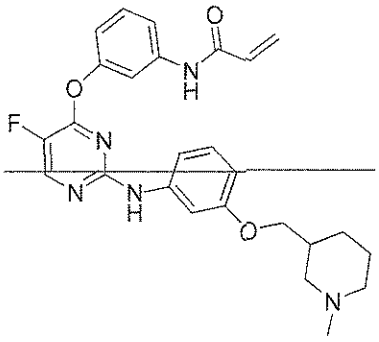
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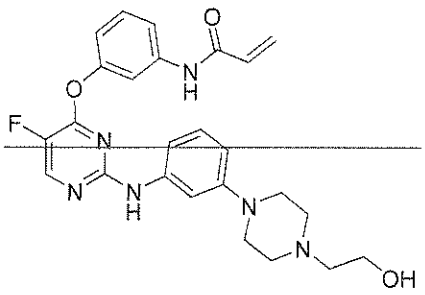
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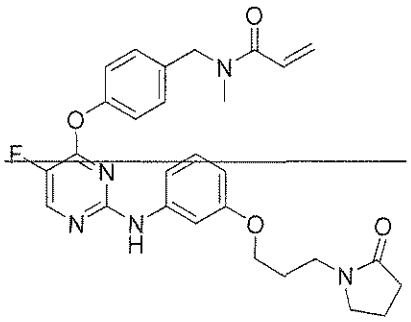
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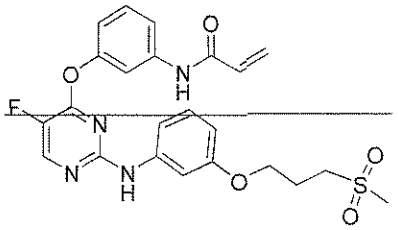
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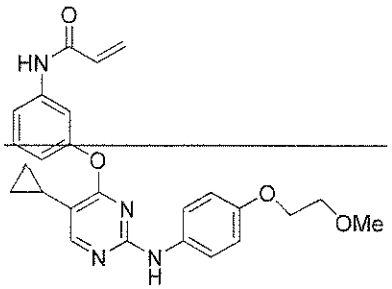
I-84



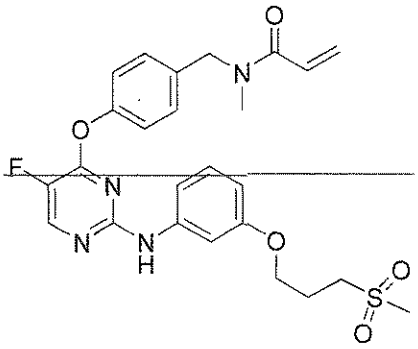
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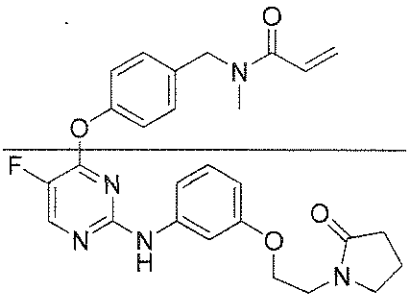
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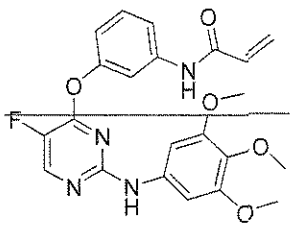
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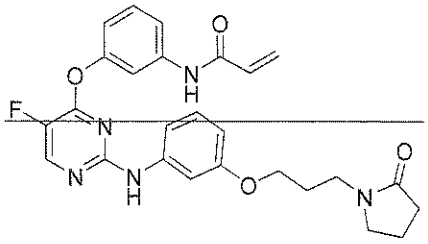
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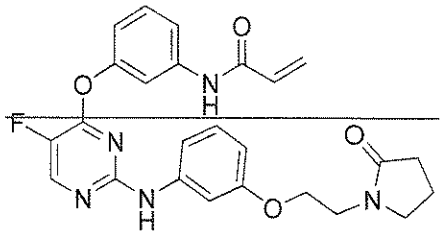
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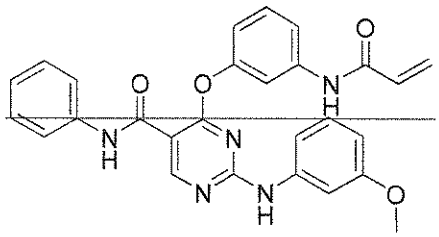
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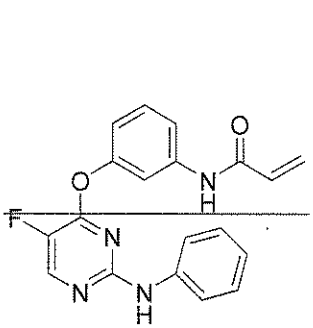
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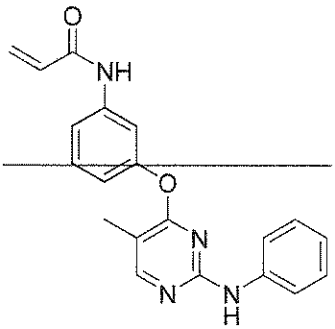
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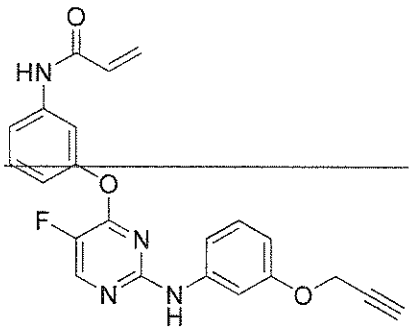
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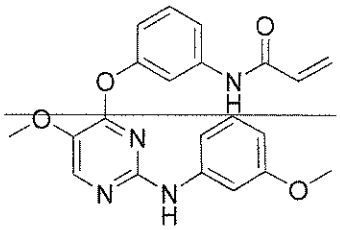
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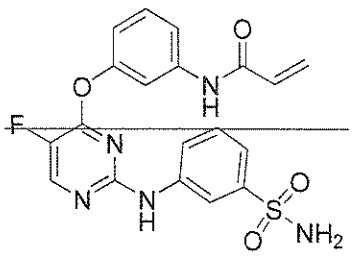
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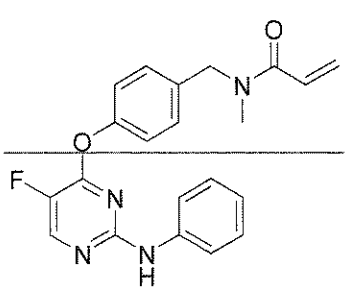
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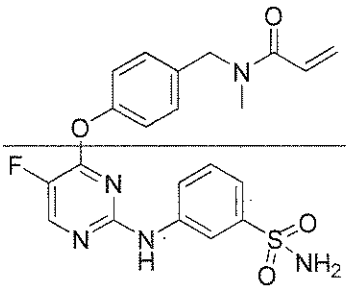
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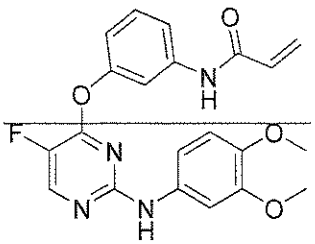
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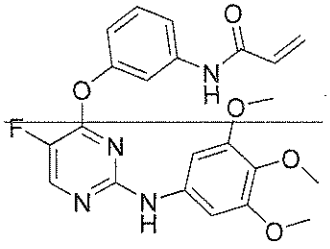
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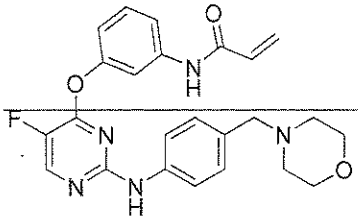
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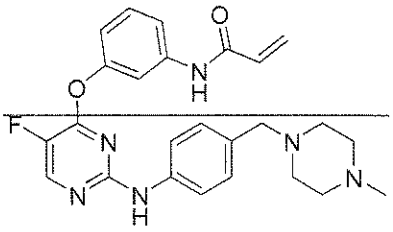
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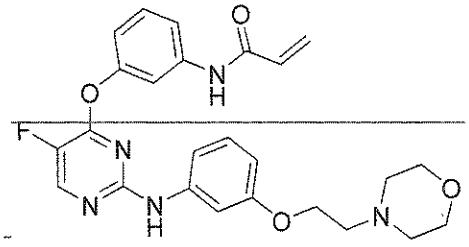
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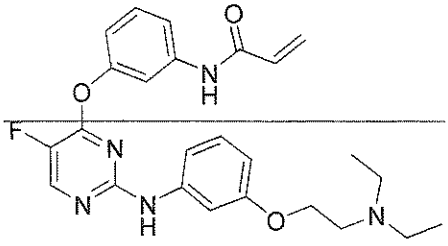
~~I-289~~



~~I-290~~



~~I-299~~



~~I-300~~

~~or a pharmaceutically acceptable salt thereof.~~

~~23~~19. The compound according to claim 1, wherein R^1 is –NHC(O)CH=CH_2.

~~24~~20. The compound according to claim ~~23~~19, wherein R^2 is hydrogen.

~~25~~21. The compound according to claim ~~24~~20, wherein Ring A is phenyl.

~~26~~22. The compound according to claim ~~25~~21, wherein Ring B is phenyl.

~~27~~23. The compound according to claim ~~26~~22, wherein at least one R^x is selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxyalkoxy, and halogen.

~~28~~24. The compound according to claim ~~27~~23, wherein at least one R^x is selected from methyl, methoxy, methoxyethoxy and fluoro.

~~29~~25. 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.~~

~~37~~26. 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.~~

~~39~~27. The composition according to claim ~~37~~26, in combination with an additional therapeutic agent.

~~40~~28. The composition according to claim ~~39~~27, wherein the additional therapeutic agent is a chemotherapeutic agent.

~~41. 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.~~

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

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

~~44~~29. 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.

~~45~~30. The use according to claim ~~44~~29, 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.

~~46~~31. The use according to claim ~~45~~30, 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.

~~47. 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.~~

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

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

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

~~51~~32. 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.

~~52~~33. The use according to claim ~~51~~32, 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.

~~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.~~

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

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

~~56~~34. 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.

~~57~~35. The use according to claim ~~56~~34, 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.

~~58~~36. The use according to claim ~~57~~35, wherein the disorder is selected from neurofibromatosis type I (NF1), neurofibromatosis type II (NF2) Schwann cell neoplasms, or a Schwannoma.

~~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.~~

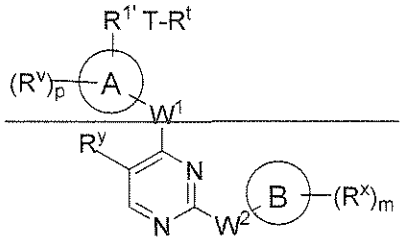
~~60. The use according to claim 59, wherein the activity of JAK3, or a mutant thereof, is inhibited irreversibly.~~

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

~~62~~37. 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.

~~63~~38. The use according to claim ~~62~~37, wherein the disorder is selected from an autoimmune disorder, an inflammatory disorder, a neurodegenerative disorder, or a solid or hematologic malignancy.

~~64. A compound of formula V-b:~~



~~V-b,~~

~~wherein:~~

~~Ring A is an optionally substitutedphenyl;~~

~~Ring B is an optionally substitutedphenyl;~~

$R^{1'}$ 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:

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;

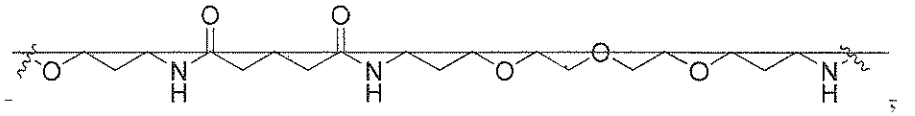
W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by -NR^2-, -N(R^2)C(O)-, -C(O)N(R^2)-, -N(R^2)SO_2-, -SO_2N(R^2)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

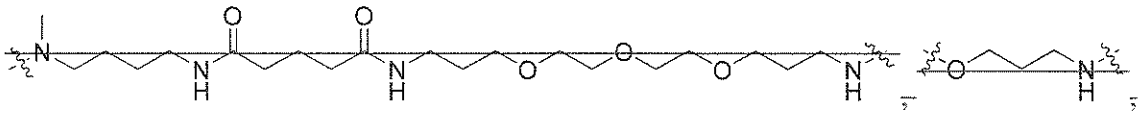
R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or -C(O)R

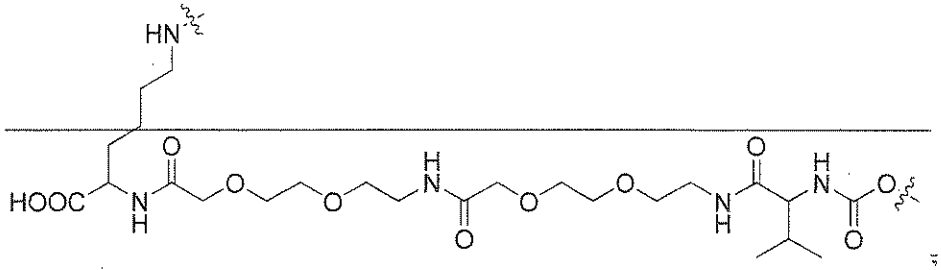
m and p are independently 0-4;

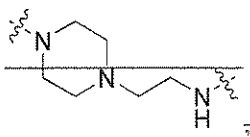
R^x and R^y are independently selected from R, halogen, OR, $O(CH_2)_qOR$, CN, NO_2, SO_2R, $SO_2N(R)_2$, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, NRC(O)R, $NRC(O)N(R)_2$, $NRSO_2R$, or $N(R)_2$, wherein q is 1-4

T is selected from

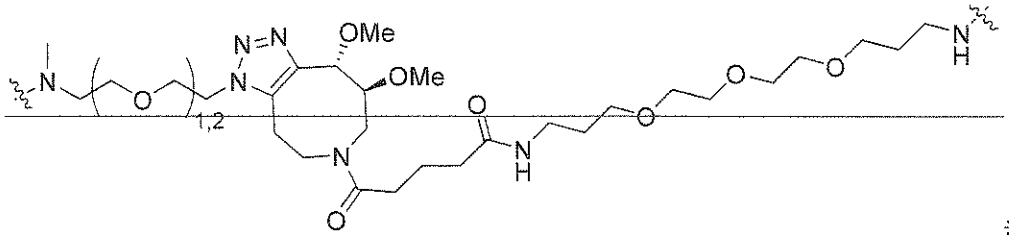








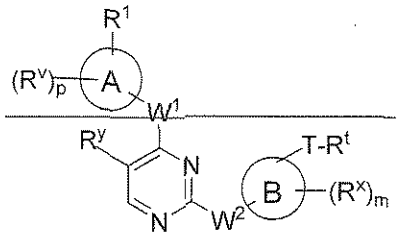
or



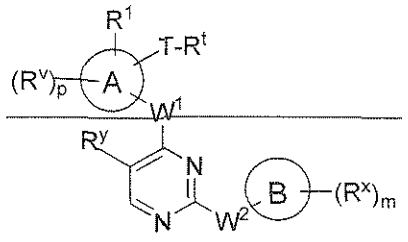
; and

R^t is a detectable moiety selected from a radioisotope, a biotin, or a fluorescent label.

65. A compound of formula VI-b or VII-b:



VI-b



VII-b,

wherein:

Ring A is an optionally substituted phenyl;

Ring B is an optionally substituted phenyl;

R^+ 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^+ is attached to an atom other than an atom adjacent to the atom attached to W^+ 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 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, $-CH_2-$, $-NH-$, $-C(O)-$, $-CH_2NH-$, $-NHCH_2-$, $-NHC(O)-$, $-NHC(O)CH_2OC(O)-$, $-CH_2NHC(O)-$, $-NHSO_2-$, $-NHSO_2CH_2-$, 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;

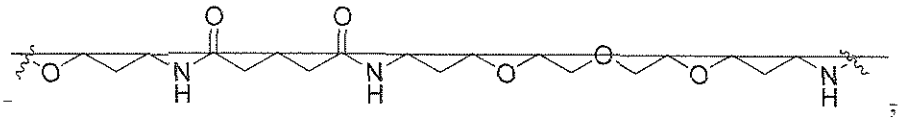
W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by $–NR^2–$, $–N(R^2)C(O)–$, $–C(O)N(R^2)–$, $–N(R^2)SO_2–$, $–SO_2N(R^2)–$, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –SO– or $–SO_2–$;

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

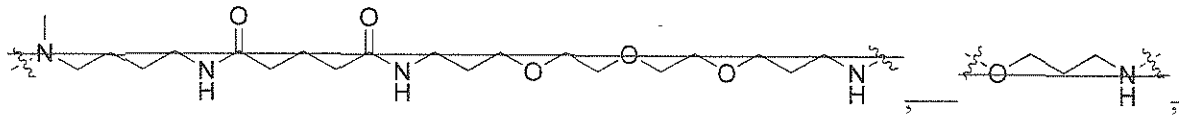
m and p are independently 0-4;

~~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;~~

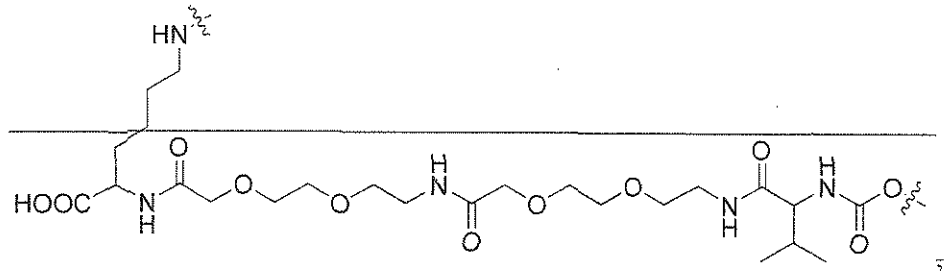
~~T is selected from~~



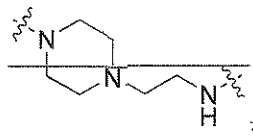
;



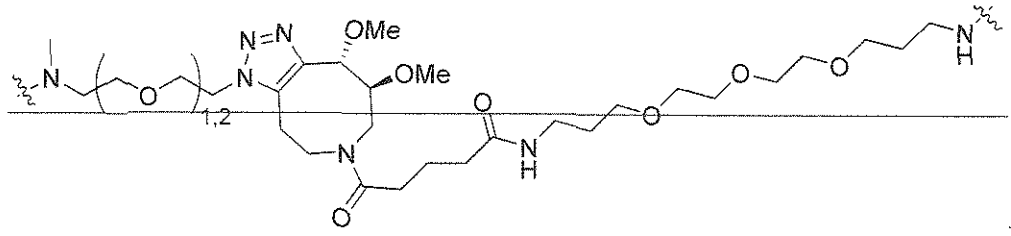
;



;



; ~~or~~



~~; and~~

~~R^t is a detectable moiety selected from a radioisotope, a biotin, or a fluorescent label.~~

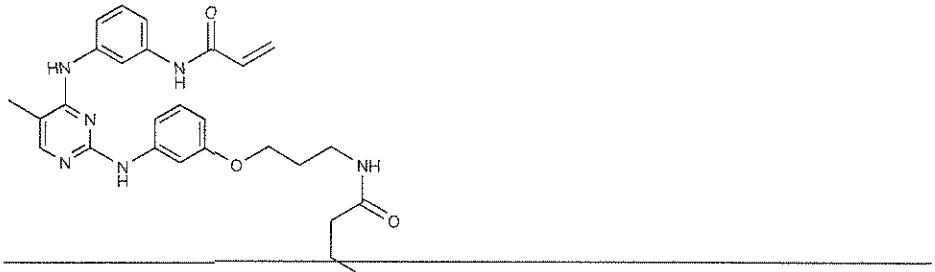
~~66. The compound of claim 64 or 65, wherein R^t is biotin.~~

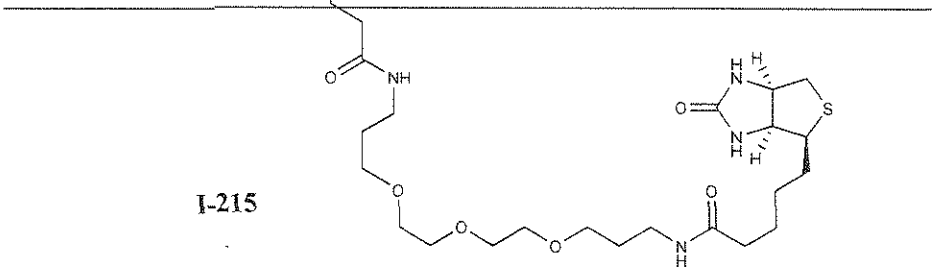
~~67. The compound of claim 64 or 65, wherein R^t is biotin sulfoxide.~~

~~68. The compound of claim 64 or 65, wherein R^t is a radioisotope.~~

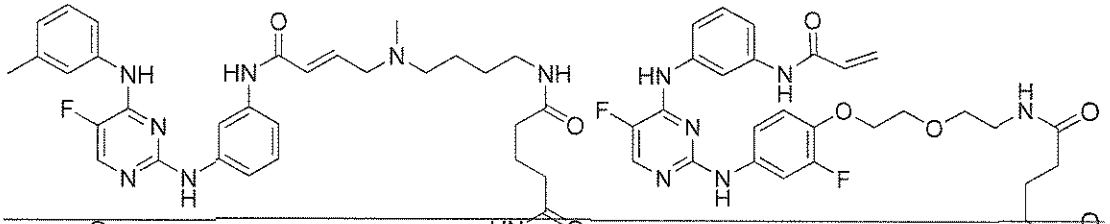
~~69. The compound of claim 64 or 65, wherein R^t is a fluorescent label.~~

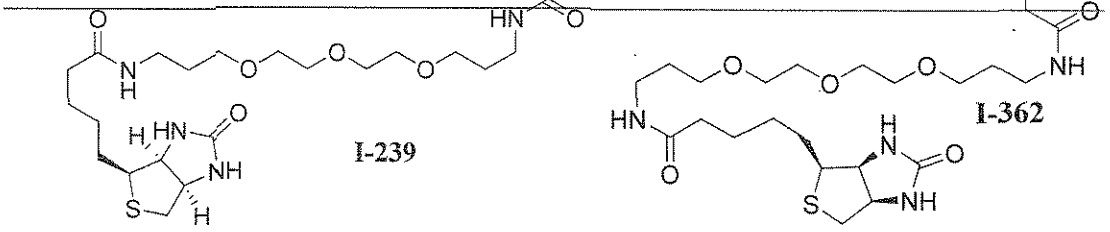
~~70. The compound of claim 64 or 65 having the structure:~~





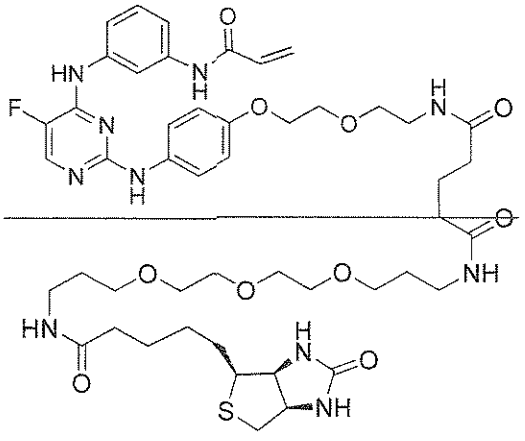
I-215



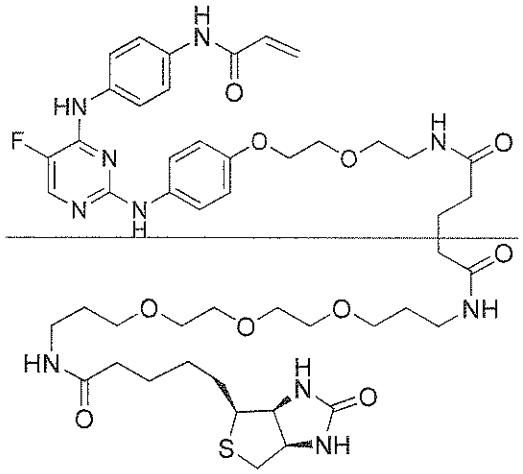


I-239

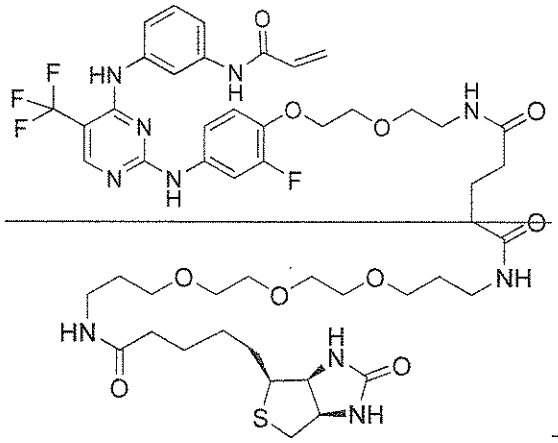
I-362



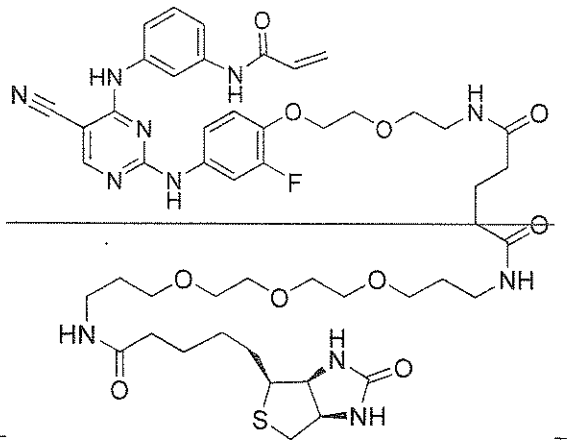
~~I-363~~



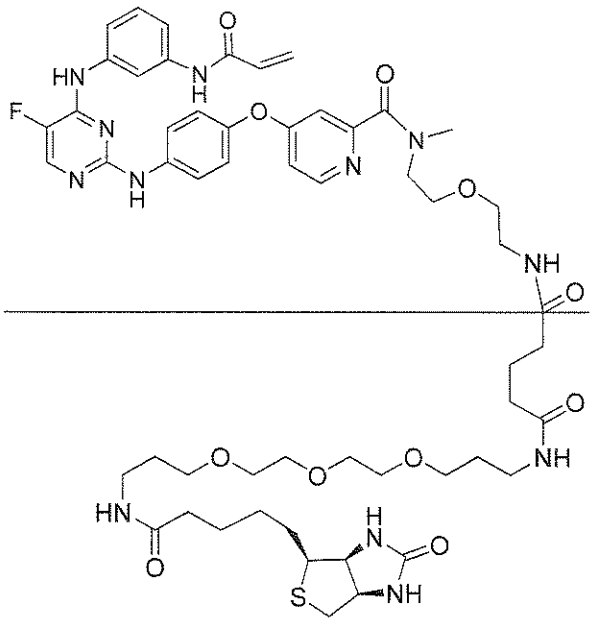
I-364



I-366



I-367



or I-368.

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.

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

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

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