CLAIMS

What is claimed is:

1. A protein kinase conjugate that has the formula,

X-M-S-CH_2-Prot

wherein, Prot is a protein kinase or portion thereof that contains a cysteine residue selected from the group consisting of CYS1, CYS5, CYS6, CYS7, CYS8, CYS9, CYS10, CYS11, CYS12 and CYS13;

wherein, if the protein kinase is JAK3, the cysteine residue is Cys945;

S-CH_2 is the sulfur atom and methylene group from the side chain of said cysteine residue;

M is a modifier moiety that is formed by the covalent bonding of a warhead group with the side chain of said cysteine residue; and

X is a chemical moiety that binds in or near the ATP binding site of the protein kinase.

2. The conjugate of claim 1, wherein the warhead group is –L-Y, wherein

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

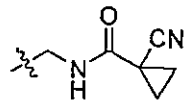
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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:

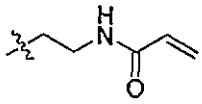
Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-;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

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

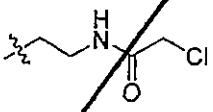
3. The conjugate of claim 1, wherein the warhead group is



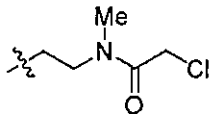
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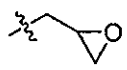
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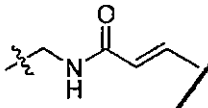
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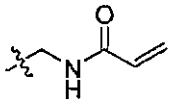
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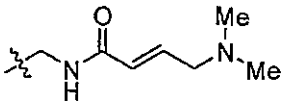
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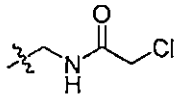
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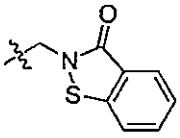
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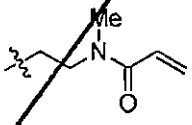
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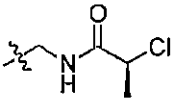
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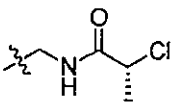
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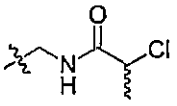
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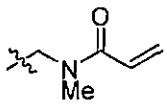
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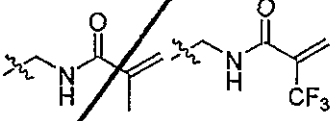
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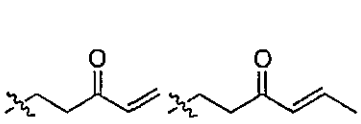
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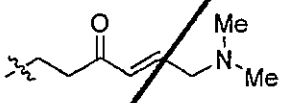
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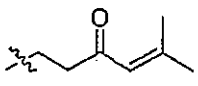
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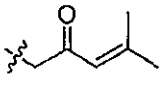
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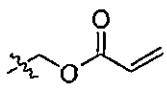
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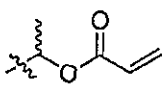
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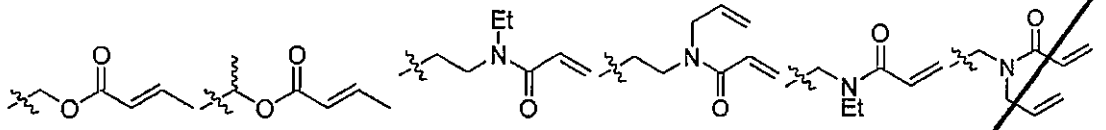
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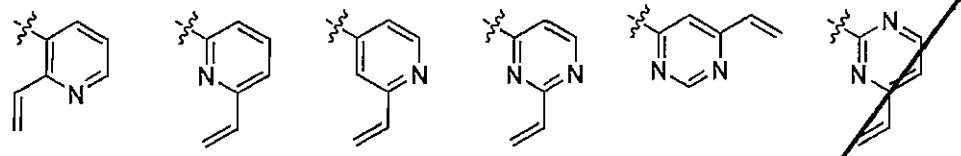
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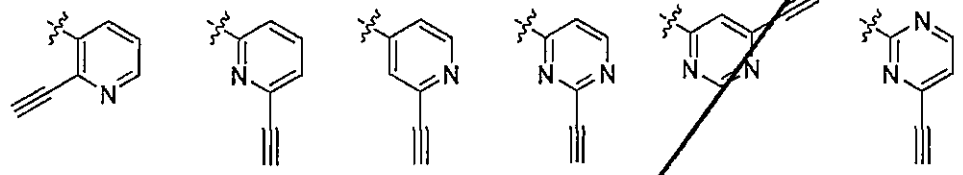
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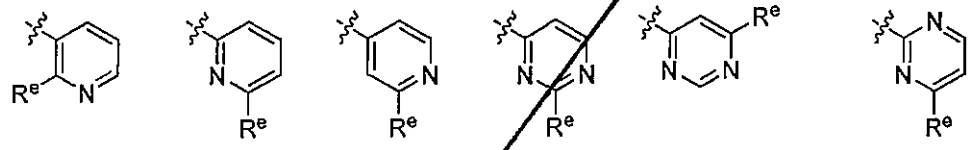
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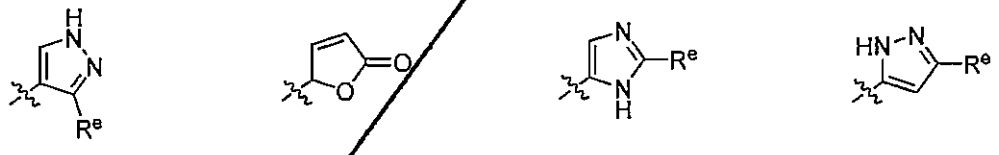
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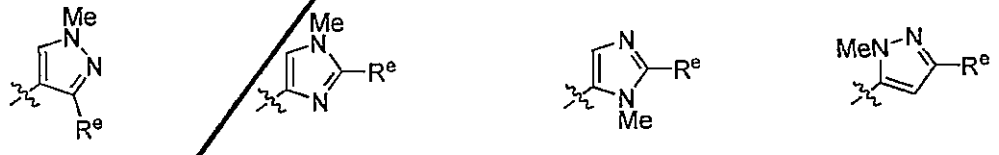
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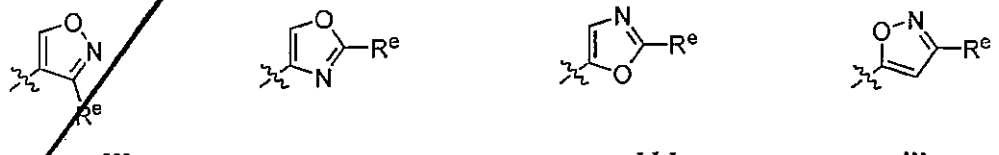
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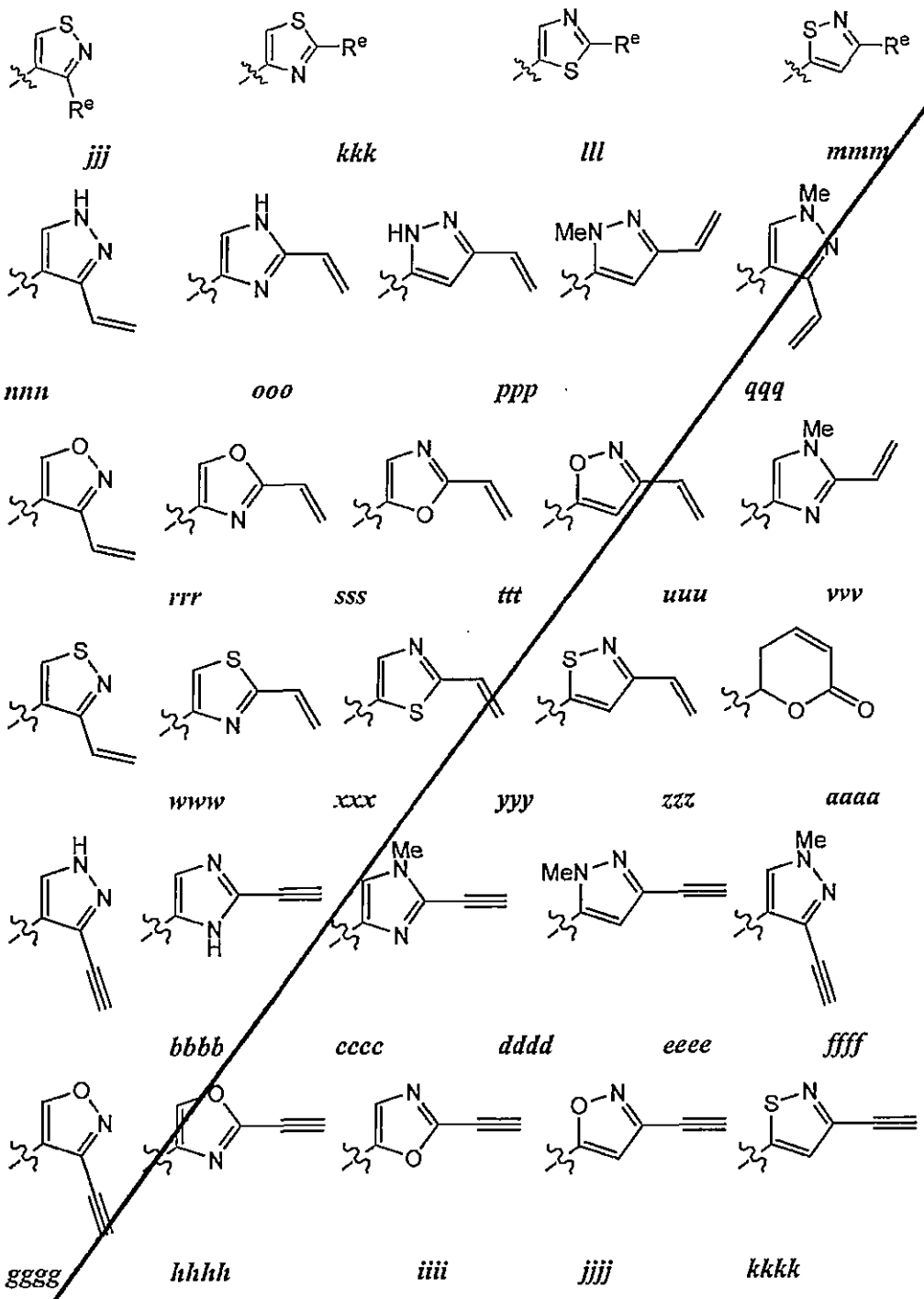
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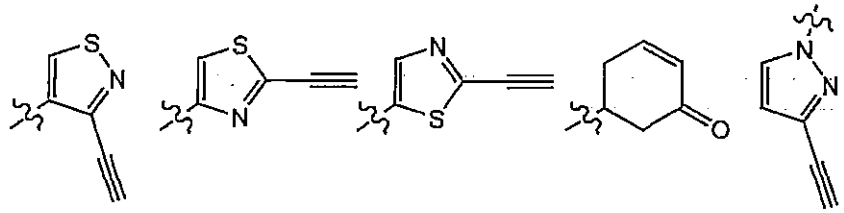


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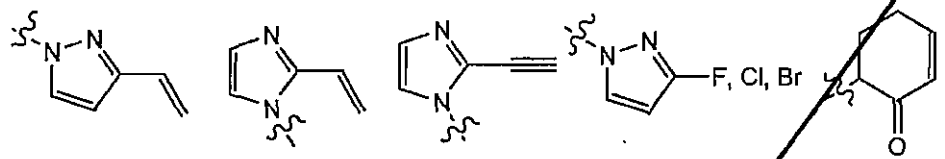


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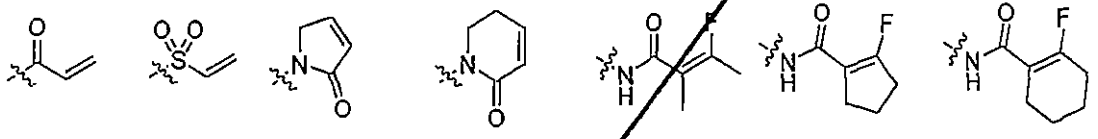

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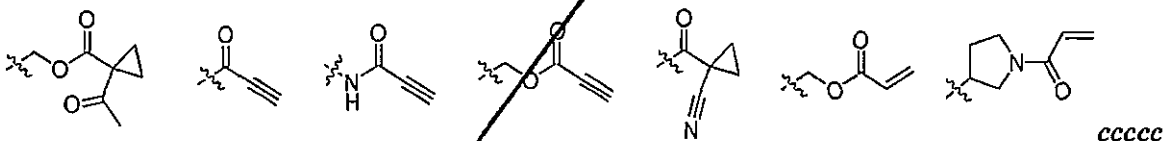
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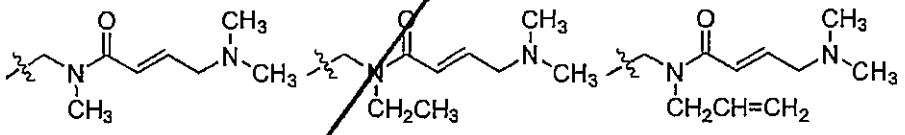
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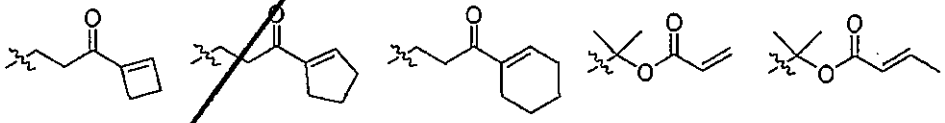
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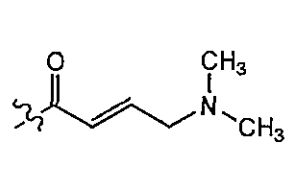
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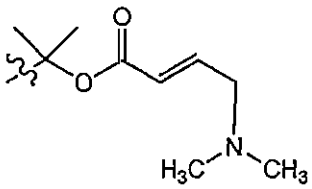
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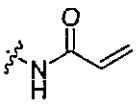
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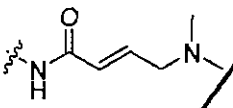
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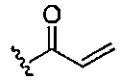
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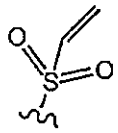
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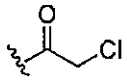
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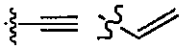
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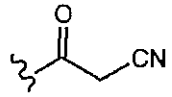
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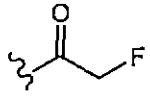
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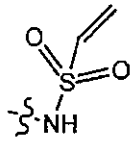
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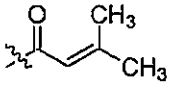
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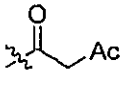
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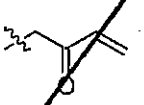
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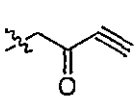
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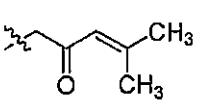
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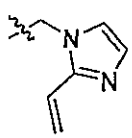
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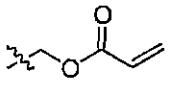
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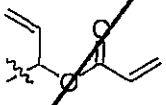
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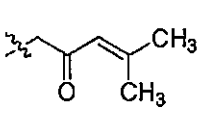
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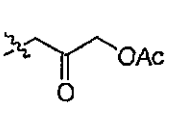
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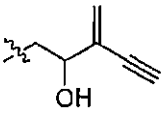
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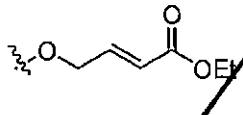
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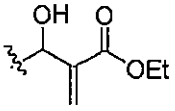
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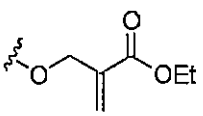
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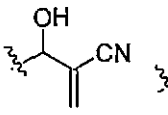
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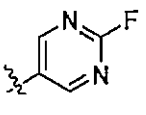
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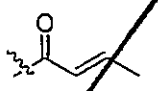
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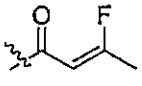


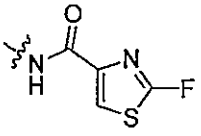
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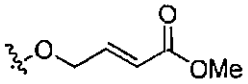


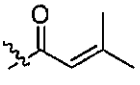
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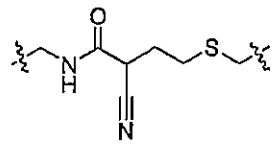




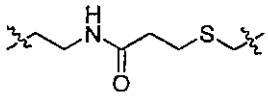
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wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

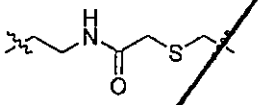
4. The conjugate of claim 1, wherein the modifier moiety taken together with the side chain Sulfur and methylene of the cysteine have a formula selected from the group consisting of



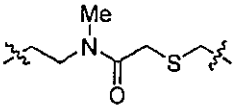
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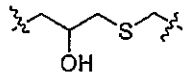
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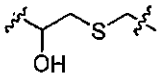
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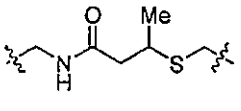
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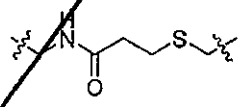
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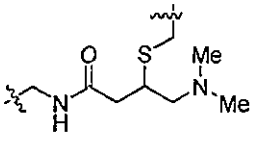
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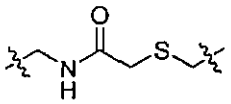
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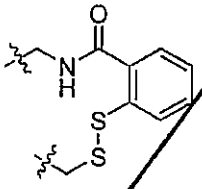
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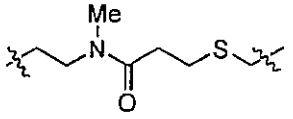
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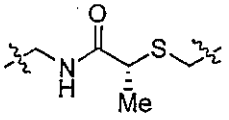
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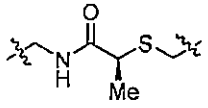
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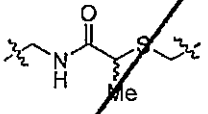
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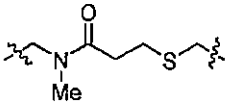
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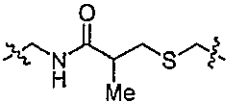
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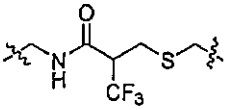
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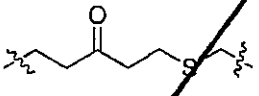
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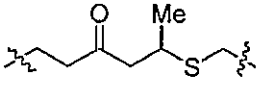
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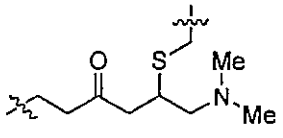
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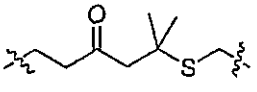
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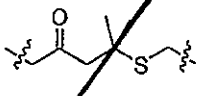
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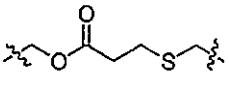
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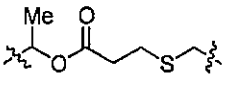
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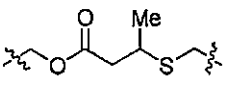
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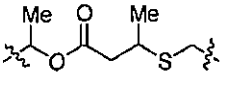
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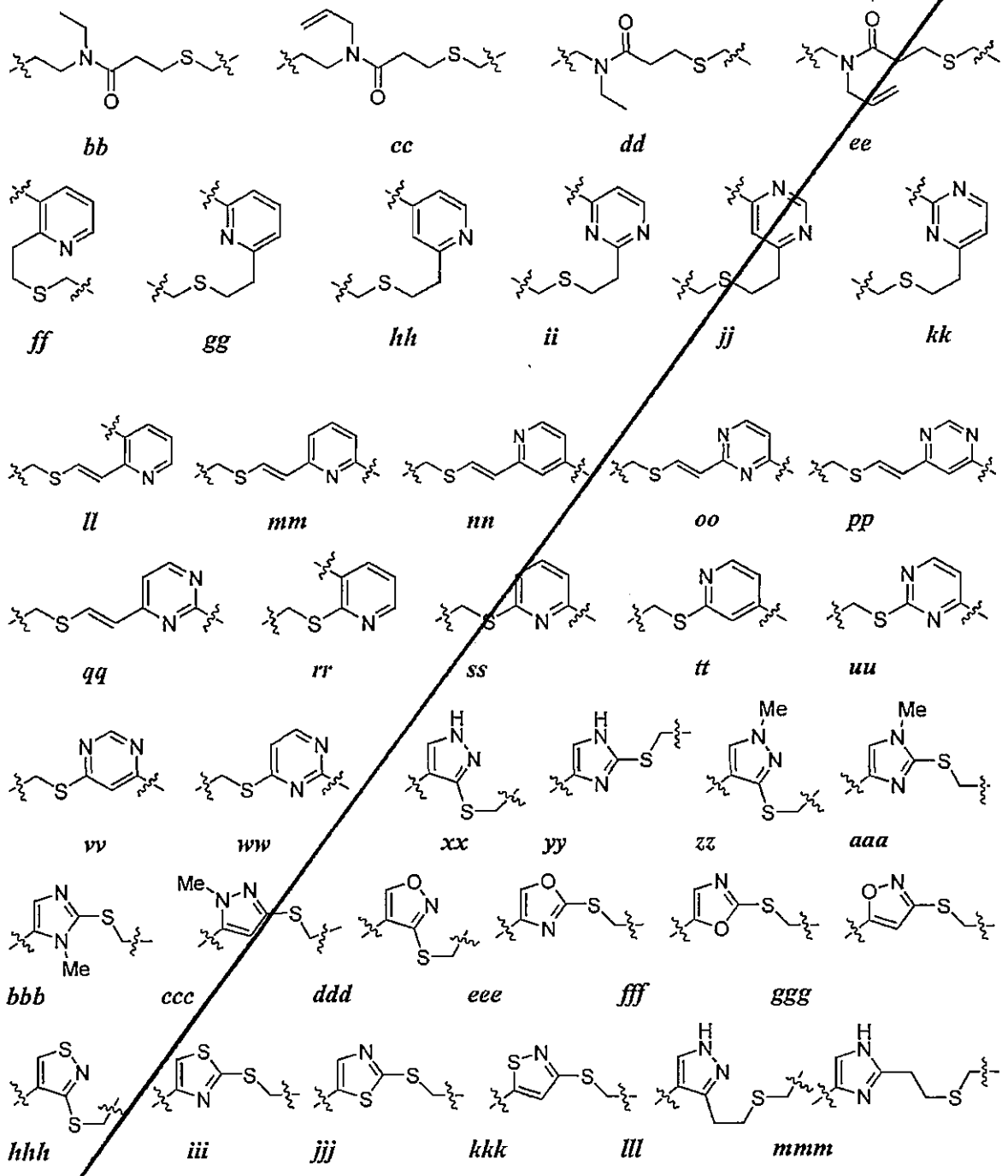
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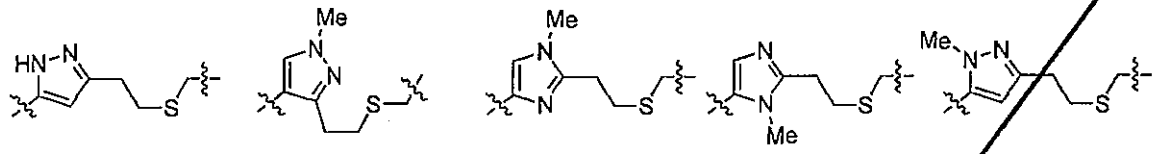


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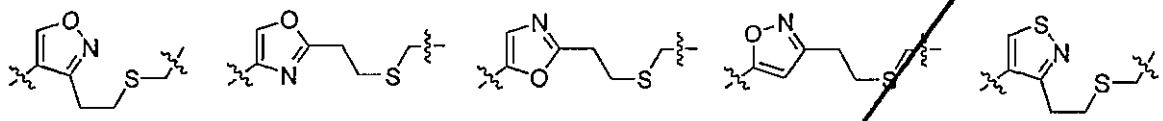


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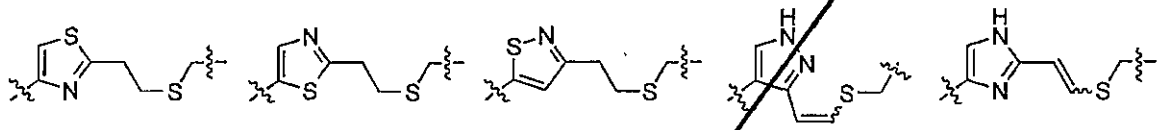

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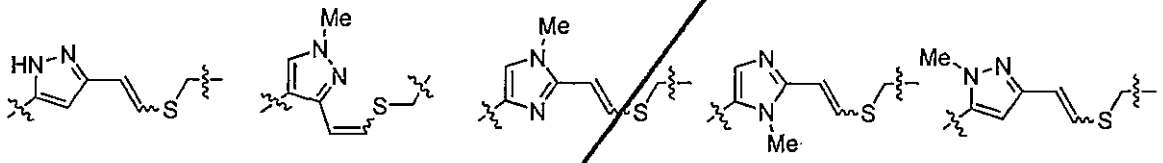
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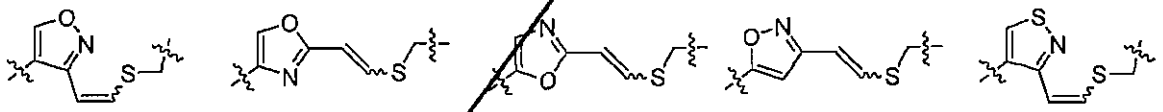
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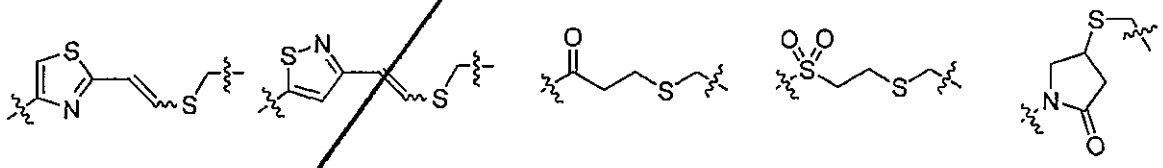
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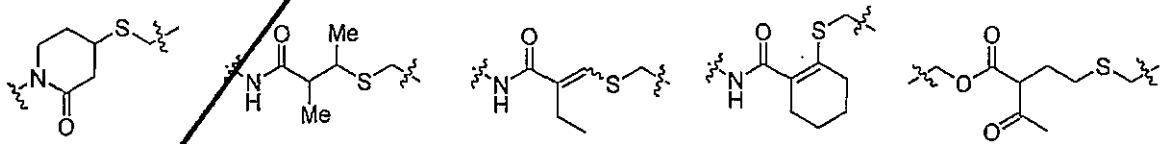
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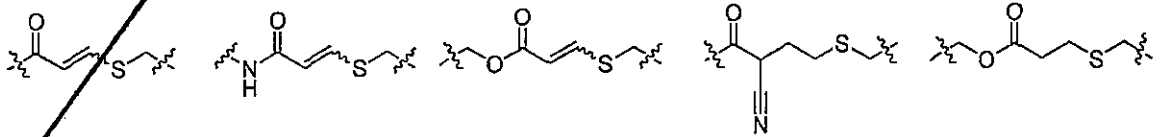
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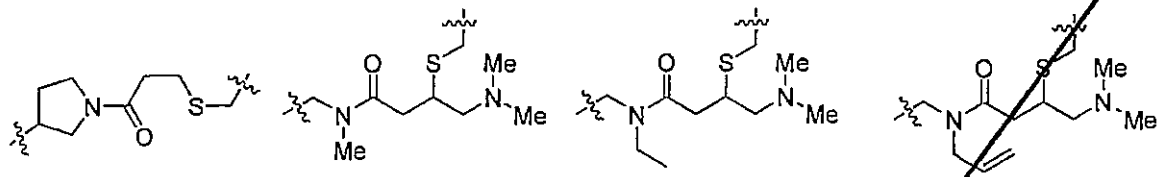
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rrrr *ssss* *tttt* *uuuu* *vvvv*



wwww *xxxx* *yyyy* *zzzz* *aaaaa*



bbbbb *ccccc* *ddddd* **and** *eeeee.*

5. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS1, and is selected from the group consisting of JAK3, FGFR1, FGFR2, FGFR3, FGFR4, CKIT, CSFR1, PDGFR-A, FAK2, FLT3, FER, FES, CDKL1, CDKL4, FLT4, KDR, FLT1, PDGFR-B, and a portion of any one of the foregoing that comprises CYS1.

6. The conjugate of claim 5, wherein Prot comprises an amino acid sequence selected from the group consisting ofRC*VHRDL, KC*IHRDL, NC*IHRDL, NC*IHRDV, NC*VHRDL, NC*VHRDI, SC*VHRDL, CC*IHRDL, or NC*IHRDI, wherein C* is CYS1.

7. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS5, and is selected from the group consisting of PFTAIRE1, JNK1, JNK2, JNK3 BMPR2, and a portion of any one of the foregoing that comprises CYS5.

8. The conjugate of claim 7, wherein Prot comprises an amino acid sequence selected from the group consisting of DLC*QYMD, NLC*QVIH, NLC*QVIQ, and SLC*KYLSL, wherein C* is CYS5.

9. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS6, and is selected from the group consisting of TNK1, YES, FGR, SRC, LIMK1, FGFR1, FGFR2, FGFR3, FGFR4, and a portion of any one of the foregoing that comprises CYS6.

10. The conjugate of claim 9, wherein Prot comprises an amino acid sequence selected from the group consisting of SGC*FGV, QGC*FGE, TGC*FGD, KGC*FGQ, and EGC*FGQ, wherein C* is CYS6.

11. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS7, and is selected from the group consisting of FAK, ALK1, ALK2, and a portion of any one of the foregoing that comprises CYS7.

12. The conjugate of claim 11, wherein Prot comprises an amino acid sequence selected from the group consisting of GRC*IGEGQFGD, VEC*VGKGRYG, and LEC*VGKGRYG, wherein C* is CYS7.

13. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS8, and is selected from the group consisting of ZAP70, CRIK, ERK3, CK1g1, CK1g2, CK1g3, and a portion of any one of the foregoing that comprises CYS8.

14. The conjugate of claim 13, wherein Prot comprises an amino acid sequence selected from the group consisting of GC*GNF, GC*GHF, and GC*GGN, wherein C* is CYS8.

15. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS9, and is ROR1or a portion thereof that comprises CYS9.

16. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS10, and is MELK or a portion thereof that comprises CYS10.

17. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS11, and is selected from the group consisting of c-KIT, FMS, RON, FLT3, FGR, and a portion of any one of the foregoing that comprises CYS11.

18. The conjugate of claim 17, wherein Prot comprises an amino acid sequence selected from the group consisting of YCC*YG, TMC*HG, and FMC*HG, wherein C* is CYS11.

19. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS12, and is ALK or a portion thereof that comprises CYS12.

20. The conjugate of claim 19, wherein Prot comprises the amino acid sequence AARNCLLTC*PGPGRVAKIGD, wherein C* is CYS12.

21. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS13, and is B-RAF or a portion thereof that comprises CYS13.

22. The conjugate of claim 21, wherein Prot comprises the amino acid sequence TKPQLAIVTQWC*EGSSLYHH, wherein C* is CYS13.

23. The protein kinase conjugate of claim 1, comprising C-KIT or a portion thereof comprising CYS1 (Cys788), and a compound of formula XVIII, XIX, XIX-a, XIX-b, XIX-c, XX or XX-a that is covalently and irreversible bonded to CYS1; or

comprising B-RAF or a portion thereof comprising CYS13 (Cys532), and a compound of formula XVIII, XIX, XIX-a, XIX-b, XIX-c, XX or XX-a that is covalently and irreversible bonded to CYS13; or

comprising FAK or a portion thereof comprising CYS7 (Cys427), and a compound of formula IV, IVa or IVb that is covalently and irreversible bonded to CYS7; or

comprising JNK1 or a portion thereof comprising CYS5 (Cys116), and a compound of formula VI, VII, VIII, IX, IX-a, X, X-a, XI, XII or XII-a that is covalently and irreversible bonded to CYS5; or

comprising ZAP70 or a portion thereof comprising CYS8 (Cys346), and a compound of formula I-a, I-b, I-c, I-d, I-e, and I-f that is covalently and irreversible bonded to CYS8; or

comprising RON or a portion thereof comprising CYS11 (Cys1165), and a compound of formula XIII-a, XIII-b, XIII-c, XIII-d, XIV, XV, XVI, or XVII that is covalently and irreversible bonded to CYS11; or

comprising a compound of formula I-a, I-b, I-c, I-d, I-e, I-f, II-a, II-b, II-c, II-d, III, IV, IVa, IVb, V, VI, VII, VIII, IX, IX-a, X, X-a, XI, XII, XII-a, XIII-a, XIII-b, XIII-c, XIII-d, XIV, XV, XVI, XVI-a, XVI-b, XVI-c, XVII, XVIII, XIX, XIX-a, XIX-b, XIX-c, XX, or XX-a.

24. A protein kinase conjugate comprising KDR or a portion thereof comprising CYS2 (Cys1045), and a compound of formula XVIII, XIX, XIX-a, XIX-b, XIX-c, XX or XX-a that is covalently and irreversible bonded to CYS2, or

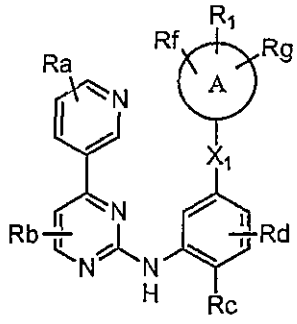
comprising FLT3 or a portion thereof comprising CYS2 (Cys828), and a compound of formula II-a, II-b, II-c or II-d that is covalently and irreversible bonded to CYS2, or

comprising MEK1 or a portion thereof comprising CYS2 (Cys207), and a compound of formula II-a, II-b, II-c or II-d that is covalently and irreversible bonded to CYS2, or

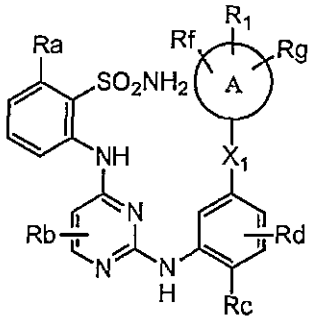
comprising JAK3 or a portion thereof comprising CYS3 (Cys909), and a compound of formula V that is covalently and irreversible bonded to CYS3, or

comprising PLK1 or a portion thereof comprising CYS4 (Cys67), and a compound of formula III that is covalently and irreversible bonded to CYS4.

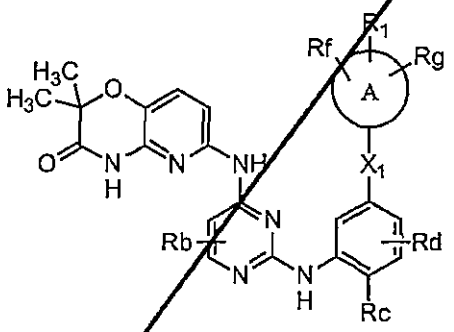
25. A compound of formula I-a, I-b or I-c



I-a



I-b



I-c

or a pharmaceutically acceptable salt thereof, wherein

each of R^aR^b, R^c, R^d, $R^f$are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R or –C(O)NHRz;

R^g *is selected from R, OR, halogen,* $-CF_3$ *anda 5-10 membered monocyclic or* bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur that is optionally substituted with R, OR, halogen or –CF3;

each R is independently hydrogen, lower alkyl, lower haloalkyl or lower cycloalkyl;

Each R' is independently hydrogen, aliphatic or aryl;

X_1 is –NH-C(O)- or –C(O)-NH-;

Ring A is a 4-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; and

R_1 is –L-Y, wherein:

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

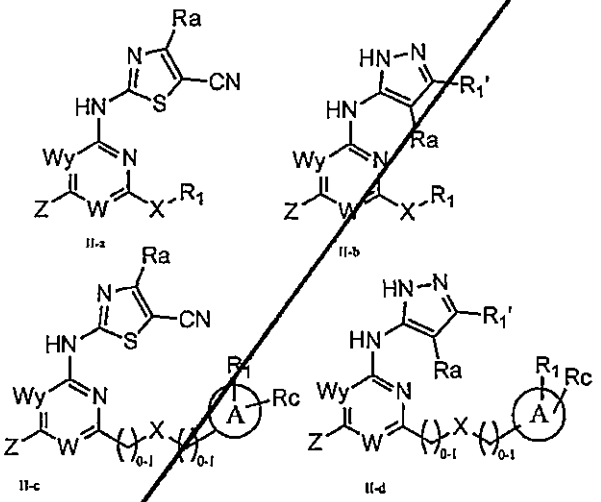
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

26. A compound of formula II-a, II-b, II-c or II-d



or a pharmaceutically acceptable salt thereof, wherein:

Wy is N or C-Rb;

W is N or CH;

X is NH, CH_2, O or S;

each of $R^a R^b$,and R^c are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, or –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

Z is hydrogen or a solubilizing group;

Ring A is a 4-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R_1 or $R_{1'}$ is –L-Y, with the proviso that when R_1 is –L-Y, $R_{1'}$ is R, OR, halogen, $-CF_3$, -CN, -C≡C-R or –C(O)NHR', and when $R_{1'}$ is –L-Y, R_1 is R, OR, halogen, $-CF_3$, -CN, -C≡C-R or –C(O)NHR';

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

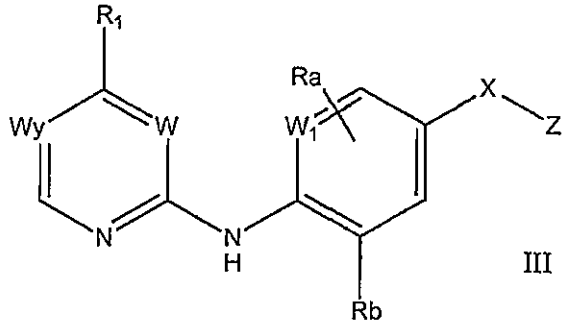
each R^e is independently selected from –Q-Z, OH, oxo, NO_2, halogen, CN, a suitable leaving group, or a C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, wherein:

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.

27. A compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein

R^a and R^b are independently selected from hydrogen, R, OR, halogen, –CF_3, -CN, -C≡C-R, -NRxRy, or –C(O)NRxRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

X a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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)-;

Z is hydrogen, lower alkyl or a 5 or 6 membered saturated, partially unsaturated or aromatic ring that contains 0-3 heteroatoms selected from N, S and O, and contains 0-3 substituents selected from the group consisting of oxo, lower alkyl, -O-lower alkyl, a halogen, and -CF3;

W and W1 are independently N or CH;

Wy is N or C-Rc

Rc is hydrogen; R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, -C(O)Rx or –C(O)NRxRz;

R_1 is –L-Y;or

Rc and R1 taken together with the atoms to which they are bonded form a 5 or 6 membered partially unsaturated or aromatic ring that contains 0-3 heteroatoms selected from N, S and O, and is substitute with –L-Y and up to two other substituents selected from the group consisting of oxo, lower alkyl, -O-lower alkyl, a halogen, and -CF3;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

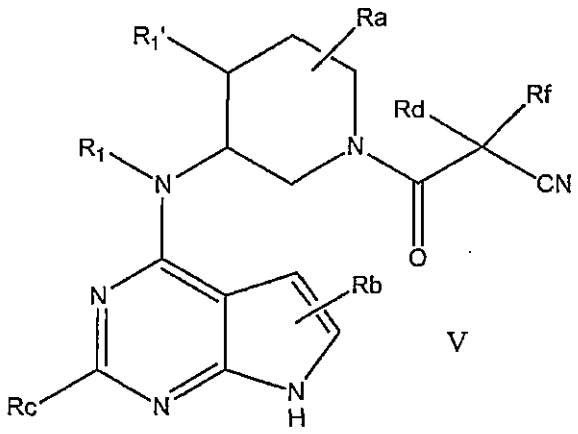
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

28. A compound of formula V:



V

or a physiologically acceptable salt thereof, wherein

R^a, R^b, Rc Rd and Rf are independently selected from hydrogen, R, OR, halogen and $-CF_3$;

each R is independently hydrogen, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkynl, or lower haloalkyl;

R_1 or $R_{1'}$ is -L-Y, with the proviso that when R_1 is -L-Y, $R_{1'}$ is hydrogen or lower alkyl, and when $R_{1'}$ is -L-Y, R_1 is hydrogen or lower alkyl;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

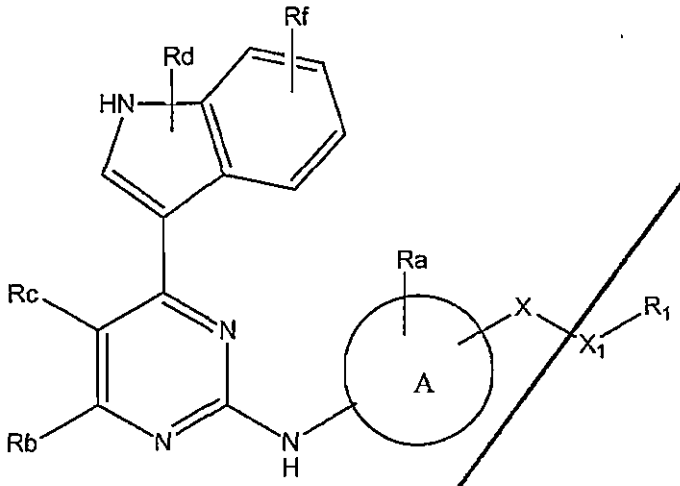
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

29. A compound of formula VI:



VI

or a pharmaceutically acceptable salt thereof, wherein

Ra, Rb, Rc, Rd and Rf are independently selected from R, OR, halogen, –CF_3, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

Ring A is a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

X is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by –NR-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(=S)-, -C(=NR)-, -N=N-, or -C(=N_2)-;

X_1 is a bond or is a bivalent 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

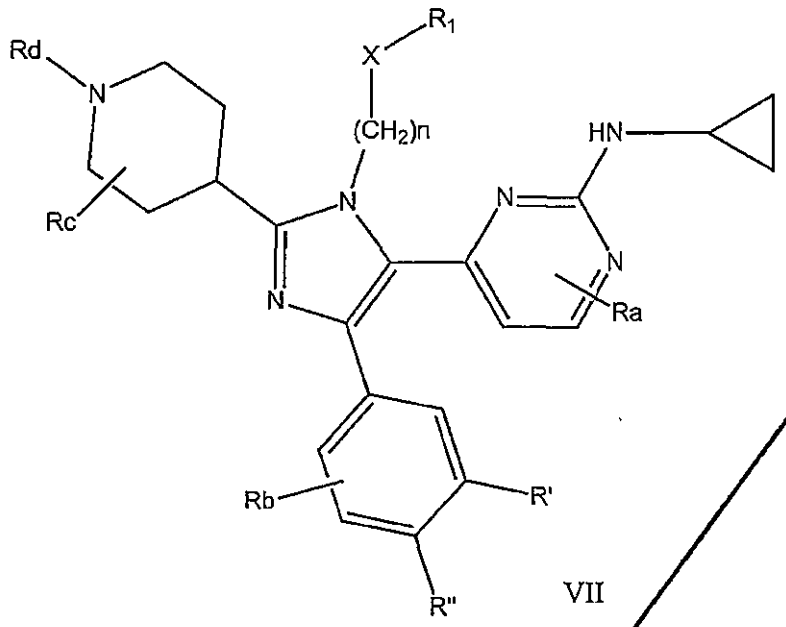
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

30. A compound of formula VII



VII

or a pharmaceutically acceptable salt thereof, wherein

n is one, two, or three;

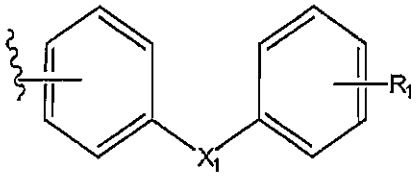
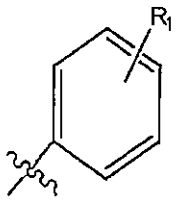
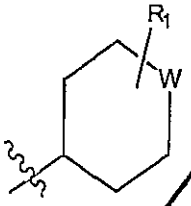
Ra, R^b, and Rc are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

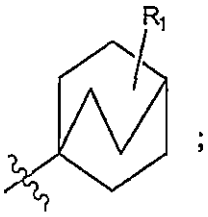
each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R'and R'' are independently hydrogen or halogen;

X is a bond, or is selected from the group consisting of




and


;

X_1 is O, NH or S;

W is CH2 or NH;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

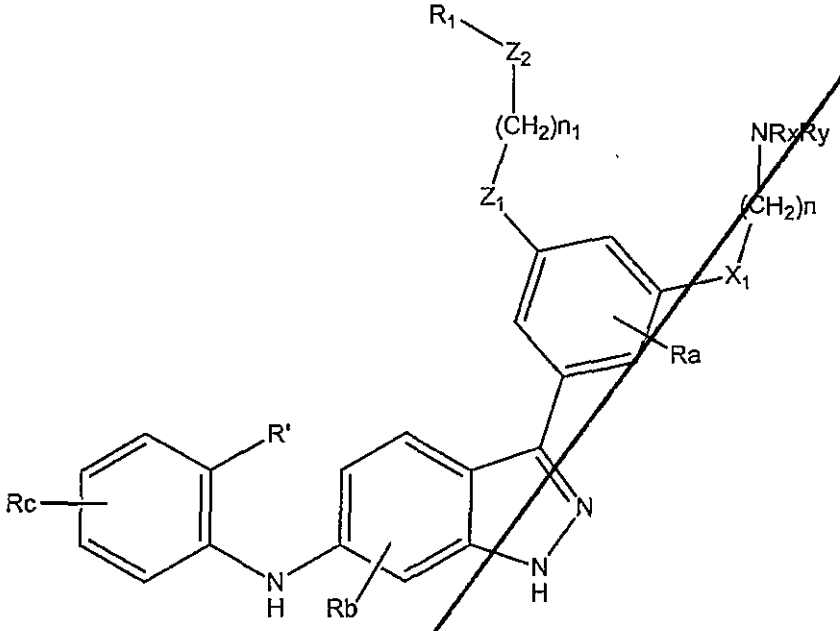
each R^e is independently selected from –Q-Z, OH, oxo, NO_2, halogen, CN, a suitable leaving group, or a C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, wherein:

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.

31. A compound of formula VIII:



VIII

or a pharmaceutically acceptable salt thereof, wherein

n and n1 are independently zero, one, two, three or four;

Ra, R^b, and Rc are independently selected from R, OR, halogen, –CF_3, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each Rz is independently hydrogen, aliphatic, or aryl;

R' is halogen;

X_1 and Z_1 are independently –N(Ry)-C(O)-, -C(O)-N(Ry)-;

Z_2 is a bond or a 4 to 10 membered monocyclic or bicyclic, saturated, partially unsaturated or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

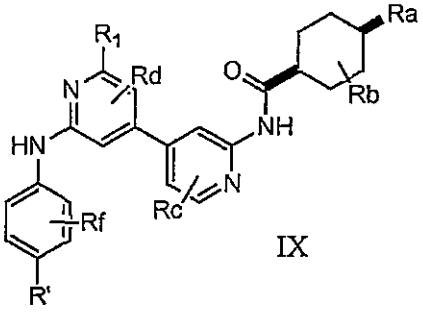
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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:

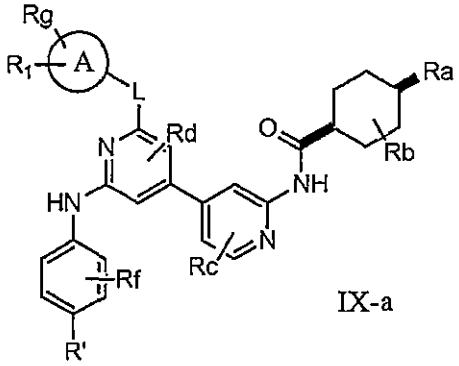
Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-;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

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

32. A compound of formula IX or IX-a:



IX



IX-a

or a pharmaceutically acceptable salt thereof, where

Ra, R^b, Rc, Rd, Rf and Rg are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R' is halogen;

Ring A is an 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

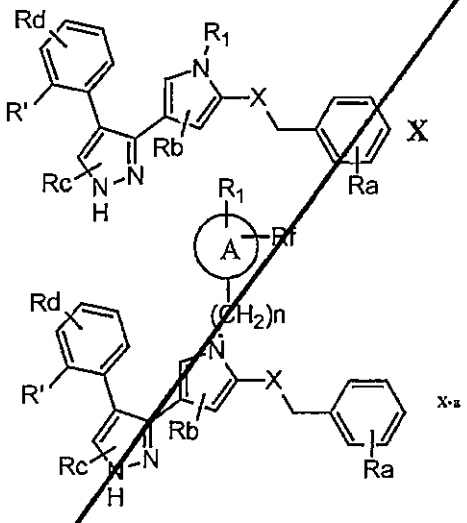
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

33. A compound of formula X or X-a:



or a pharmaceutically acceptable salt thereof, wherein

n is one, two, or three;

Ra, R^b, Rc, Rd and Rf are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R' is a halogen;

X is –C(O)NRx- or –NRx-C(O)-"

Ring A is a 4-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

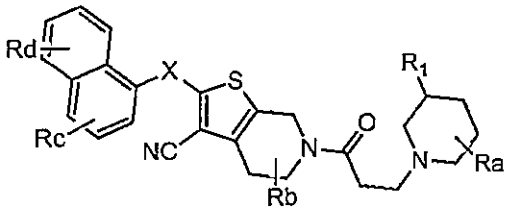
each R^e is independently selected from –Q-Z, OH, oxo, NO_2, halogen, CN, a suitable leaving group, or a C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, wherein:

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.

34. A compound of formula XI:



XI

or a pharmaceutically acceptable salt thereof, wherein

Ra, R^b, Rc and Rd are independently selected from R, OR, halogen, –CF_3, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

X is –C(O)NRx- or –NRx-C(O)-;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

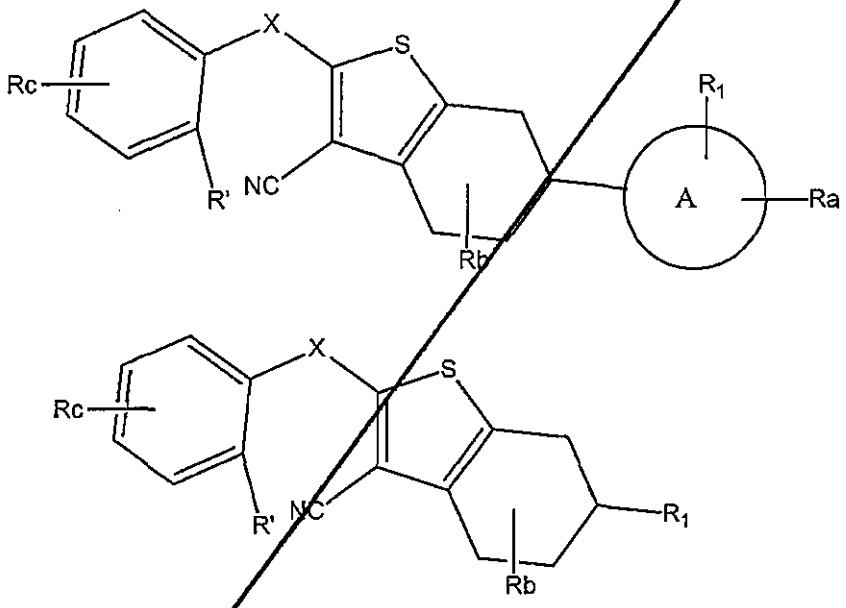
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

35. A compound of formula XII or XII-a:



or a pharmaceutically acceptable salt thereof, wherein

Ra, R^b, and Rc are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R' is a halogen;

X is –C(O)NRx- or –NRx-C(O)-'

Rx is hydrogen or lower alkyl;

Ring A is a 4-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

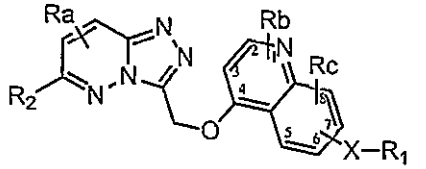
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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:

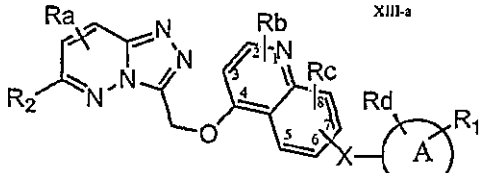
Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-;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

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

36. A compound of formula XIII-a or XIII-b:



XIII-a



XIII-b

or a pharmaceutically acceptable salt thereof, wherein

Ra, Rb, Rc and Rd are independently selected from hydrogen, R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R_2 is hydrogen optionally substituted aryl, or optionally substituted heteroaryl;

X is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by –NR-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, $-SO_2$-, -C(=S)-, -C(=NR)-, -N=N-, or -C(=N_2)-;

Ring A is a 4-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

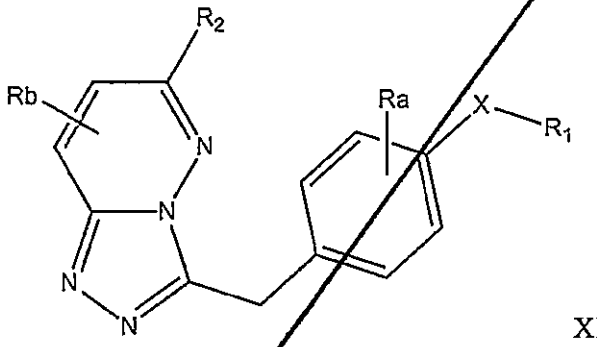
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

37. A compound of formula XIV:



XIV

or a pharmaceutically acceptable salt thereof, wherein

Ra, and Rb are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R_2 is hydrogen, optionally substituted aryl, or optionally substituted heteroaryl;

X is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by –NR-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, $-SO_2$-, -C(=S)-, -C(=NR)-, -N=N-, or $-C(=N_2)$-;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

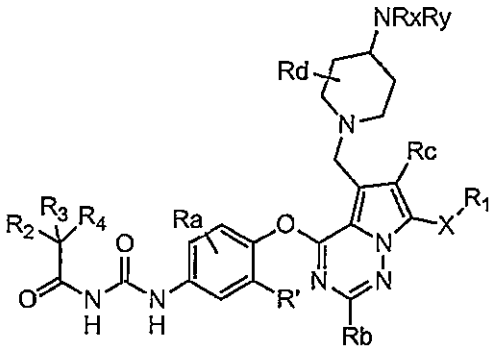
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

38. A compound of formula XV:



XV

or a pharmaceutically acceptable salt thereof, wherein

Ra, Rb, and Rc are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R_2 is hydrogen optionally substituted aryl, or optionally substituted heteroaryl;

R_3 and R_4 are independently hydrogen, R, OR, -OH, or halogen;

R' is halogen;

X is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by –NR-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, $-SO_2$-, -C(=S)-, -C(=NR)-, -N=N-, or $-C(=N_2)$-;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

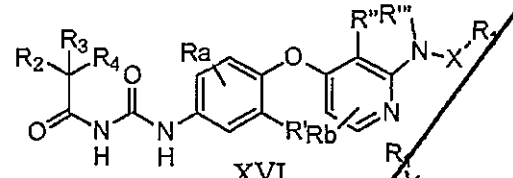
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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:

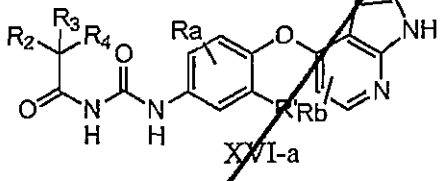
Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-;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

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

39. A compound of formula XVI or XVI-a:



XVI



XVI-a

or a pharmaceutically acceptable salt thereof, wherein

Ra and Rb are independently selected from R, OR, halogen, –CF_3, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R_2 is hydrogen optionally substituted aryl, or optionally substituted heteroaryl;

R_3 and R_4 are independently hydrogen, R, OR, -OH, or halogen;

R' is halogen;

R'' and R''' are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz,

X is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by –NR-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, $-SO_2$-, -C(=S)-, -C(=NR)-, -N=N-, or -C(=N_2)-;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

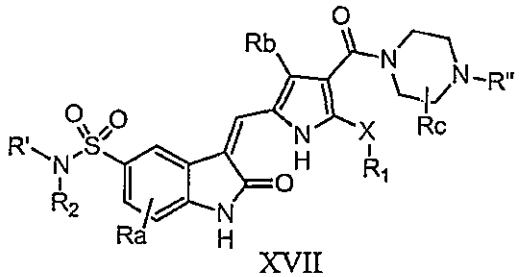
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

40. A compound of formula XVII:



XVII

or a pharmaceutically acceptable salt thereof, wherein

Ra, Rb, and Rc are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

R_2 is hydrogen, lower alkyl, lower haloalkyl, lower cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

R' and R'' are independently hydrogen or lower alkyl;

X is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by –NR-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, $-SO_2$-, -C(=S)-, -C(=NR)-, -N=N-, or $-C(=N_2)$-;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

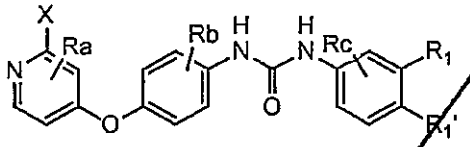
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

41. A compound of formula XVIII:



XVIII

or a pharmaceutically acceptable salt thereof, wherein

Ra, Rb, and Rc are independently selected from hydrogen, R, OR, halogen, –CF_3, -O-CF3, -CN, -C≡C-R, -NRxRy, –C(O)NHRz and 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;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

X is –C(O)-NRxRy-, or –NRxRy-C(O)-Rz;

R_1 or $R_{1'}$ is –L-Y; with the proviso that when R_1 is –L-Y, $R_{1'}$ is selected from hydrogen, R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, –C(O)NHRz and 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, and when $R_{1'}$ is –L-Y, R_1 is selected from hydrogen, R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy,–C(O)NHRz and 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;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

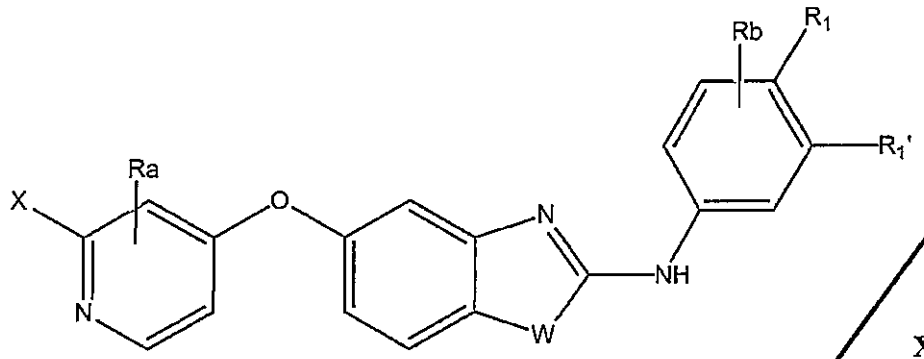
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

42. A compound of formula XIX:



XIX

or a pharmaceutically acceptable salt thereof, wherein

Ra and Rb are independently selected from hydrogen, R, OR, halogen, $-CF_3$, -O-CF3, -CN, -C≡C-R, -NRxRy,–C(O)NHRz and 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;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

X is –C(O)-NRxRy or –NRx-C(O)-Rz;

W is O, NH or N-Rc;

Rc is hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

R_1 or R_1' is –L-Y; with the proviso that when R_1 is –L-Y, R_1' is selected from hydrogen, R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, –C(O)NHRz and 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, and when R_1' is –L-Y, R_1 is selected from hydrogen, R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy,–C(O)NHRz and 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;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

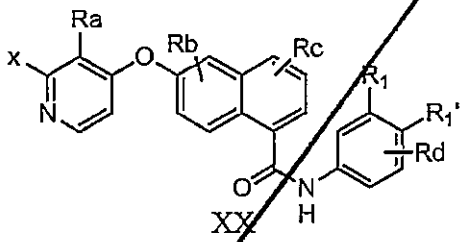
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

43. A compound of formula XX:



XX

or a pharmaceutically acceptable salt thereof, wherein

Ra, Rb, Rc and Rd are independently selected from hydrogen, R, OR, halogen, –CF_3, -O-CF3, -CN, -C≡C-R, -NRxRy, –C(O)NHRz and 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 optionally substituted with 1-4 substituents

selected from lower alkyl, lower haloalkyl, lower cycloalkyl, lower alkoxy, lower haloalkoxy, lower cycloalkoxy, $-CF_3$, -O-CF3, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

eachRz is independently hydrogen, aliphatic, or aryl;

X is –C(O)-NRxRy or –NRx-C(O)-Rz;

Or Ra and X taken together with the atoms to which they are bonded form a benzo ring that is optionally substituted one or more of Rf, Rf1. Rf2 and Rf3;

Rf, Rf1, Rf2 and Rf3 are independently selected from lower alkyl, lower haloalkyl, lower cycloalkyl, lower alkoxy, lower haloalkoxy, lower cycloalkoxy, $-CF_3$, -O-CF3, -CN, -C≡C-R, -NRxRy, and –C(O)NHRz;

R_1 or $R_{1'}$ is –L-Y; with the proviso that when R_1 is –L-Y, $R_{1'}$ is selected from hydrogen, R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, –C(O)NHRz and 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 optionally substituted with 1-4 R, and when $R_{1'}$ is –L-Y, R_1 is selected from hydrogen, R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy,–C(O)NHRz and 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 optionally substituted with 1-4 R;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

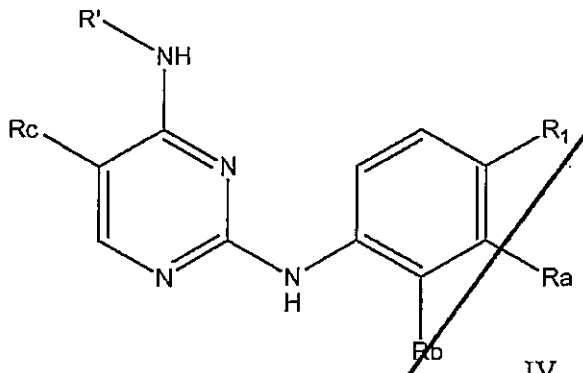
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.

44. A compound of formula IV:

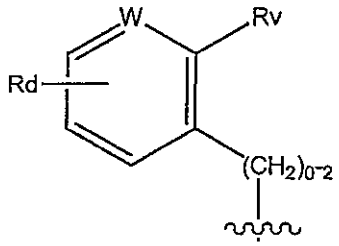


IV

or a physiologically acceptable salt thereof, wherein

Ra, Rb and Rc are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, or –C(O)NRxRz;

R' is



W is CH or N;

Rd is hydrogen, lower alkyl, -O-lower alkyl, $-CF_3$,or a halogen;

Rv is –C(O)NRxRy, -N(Rx)C(O)Rz; $-S(O)_2NRxRy$, or $-N(Rx)S(O)_2Rz$;

R_1 is –T-L-Y; or

Ra and R_1 taken together with the intervening carbon atoms to which they are bonded form a 5 or 6 membered partially unsaturated or aromatic ring that contains 0-3 heteroatoms selected from N, S and O, and is substituted with –L-Y and up to two other substituents selected from the group consisting of oxo, lower alkyl, -O-lower alkyl, a halogen, and $-CF_3$.

T is absent or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein said ring is optionally substituted with 1-4 R^e groups;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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, and sulfur, and wherein said ring is optionally substituted with 1-4 R^e groups;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

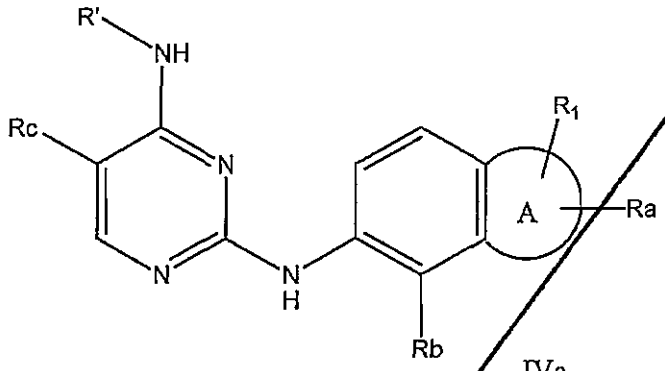
eachRz is independently hydrogen, aliphatic, or aryl;

each R^e is independently selected from –Q-Z, OH, 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.

45. A compound of formula IVa:



IVa

or a physiologically acceptable salt thereof, wherein

Ra, Rb and Rc are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, or –C(O)NRxRz;

Ring A is a 5 or 6 membered partially unsaturated or aromatic ring that contains 0-3 heteroatoms selected from N, S and O;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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)-;

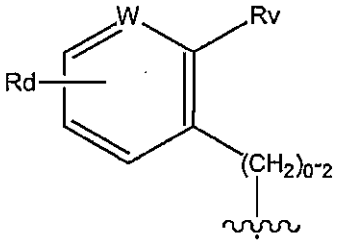
Y is hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and wherein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

each R^e is independently selected from –Q-Z, OH, 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)-;

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

R' is



W is CH or N;

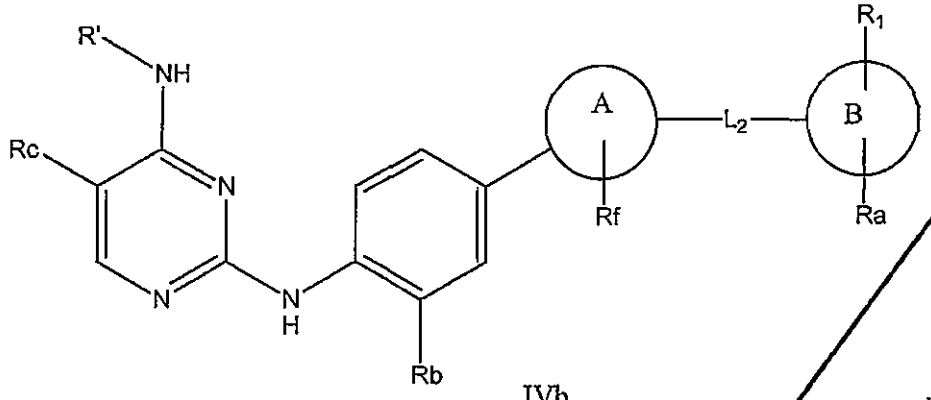
Rd is hydrogen, lower alkyl, -O-lower alkyl, -CF_3,or a halogen; and

Rv is –C(O)NRxRy, -N(Rx)C(O)Rz; -$S(O)_2$NRxRy, or –N(Rx)$S(O)_2$Rz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl; and

eachRz is independently hydrogen, aliphatic, or aryl.

46. A compound of formula IVb



IVb

or a physiologically acceptable salt thereof, wherein

Ra, Rb and Rc are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, or –C(O)NRxRz;

L_2 is a absent, a covalent bond, a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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)-, with the proviso that when L_2 is absent, Ring A and Ring B are fused or joined through a spiro atom;

Ring A and Ring B are independently a 5 or 6 membered saturated, partially unsaturated or aromatic ring that contains 0-3 heteroatoms selected from N, S and O;

R_1 is –L-Y;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially

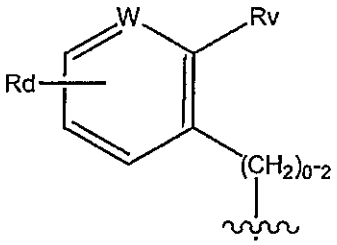
unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and wherein said ring is optionally substituted with 1-4 R^e groups;

each R^e is independently selected from –Q-Z, OH, 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 $-SO_2N(R)-$;

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

R' is



W is CH or N;

Rd is hydrogen, lower alkyl, -O-lower alkyl, $-CF_3$,or a halogen; and

Rv is –C(O)NRxRy, -N(Rx)C(O)Rz; $-S(O)_2NRxRy$, or $-N(Rx)S(O)_2Rz$;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl; and

eachRz is independently hydrogen, aliphatic, or aryl.

47. A pharmaceutical composition comprising a compound of any one of claims 25-46 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

48. An irreversible inhibitor of an angiogenesis target for use in treating an angiogenesis-related disease.

49. The irreversible inhibitor of 48, wherein the angiogenesis-related disease is an angiogenesis-related ocular disease.

50. The irreversible inhibitor of claim 48, wherein the angiogenesis target is selected from the group consisting of VEGF Receptor 2/KDR, PDGFR, SRC, FAK, PI3K, MEK, FGFR, Eph receptors, methionine aminopeptide-2 and Hsp90.

51. The use of an irreversible inhibitor of an angiogenesis target in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of an angiogenesis-related disease.

52. The use of claim 51, wherein the angiogenesis-related disease is an angiogenesis-related ocular disease.

53. The use of claim 51, wherein the angiogenesis target is selected from the group consisting of VEGF Receptor 2/KDR, PDGFR, SRC, FAK, PI3K, MEK, FGFR, Eph receptors, methionine aminopeptide-2 and Hsp90.

CLAIMS

WHAT IS CLAIMED IS:

1. A protein kinase conjugate that has the formula,

X-M-S-CH_2-Prot

wherein, Prot is a protein kinase or portion thereof that contains a cysteine residue selected from the group consisting of CYS1, CYS5, CYS6, CYS7, CYS8, CYS9, CYS10, CYS11, CYS12 and CYS13;

wherein, if the protein kinase is JAK3, the cysteine residue is Cys945;

S-CH_2 is the sulfur atom and methylene group from the side chain of said cysteine residue;

M is a modifier moiety that is formed by the covalent bonding of a warhead group with the side chain of said cysteine residue; and

X is a chemical moiety that binds in or near the ATP binding site of the protein kinase.

2. The conjugate of claim 1, wherein the warhead group is –L-Y, wherein

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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)-, -CH(OH)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(=S)-, -C(=NR)-, -N=N-, or -C(=N_2)-;

Y is hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

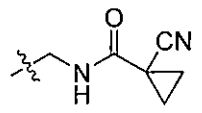
Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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:

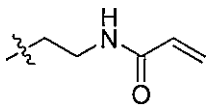
Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-;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

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

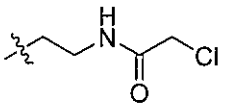
3. The conjugate of claim 1, wherein the warhead group is



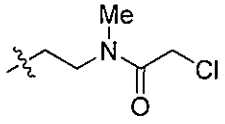
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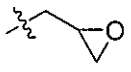
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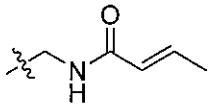
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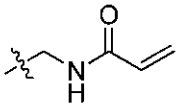
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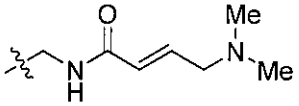
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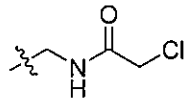
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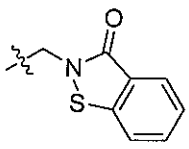
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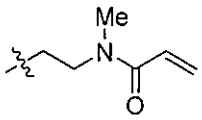
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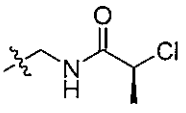
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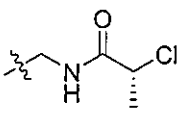
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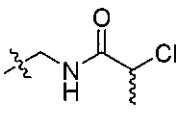
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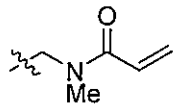
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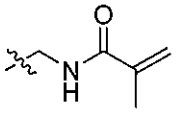
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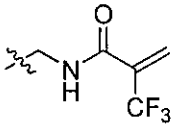
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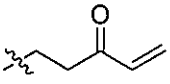
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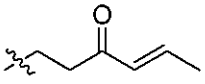
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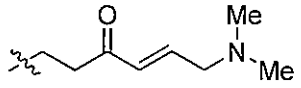
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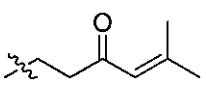
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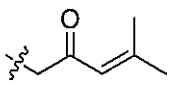
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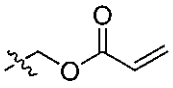
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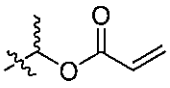
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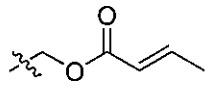
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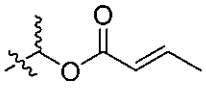
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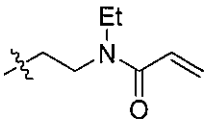
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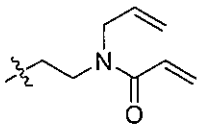
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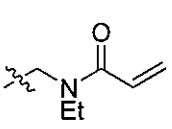
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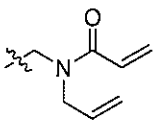
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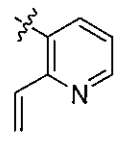
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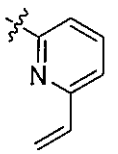
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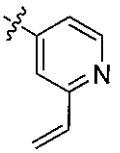
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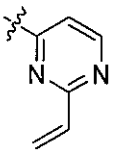
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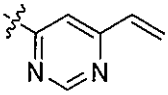
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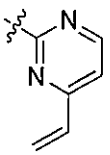
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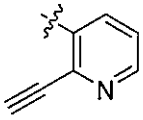
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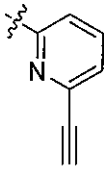
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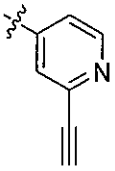
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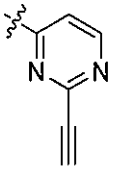
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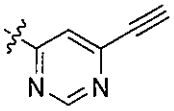
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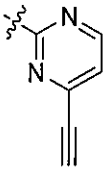
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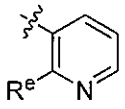
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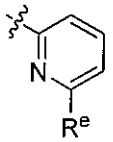
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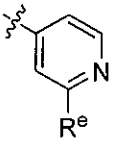
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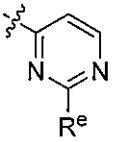
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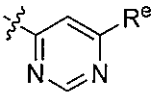
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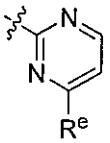
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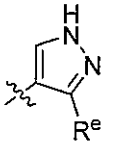
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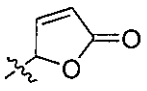
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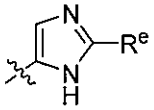
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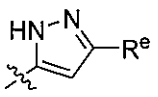
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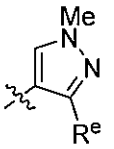
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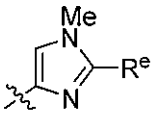
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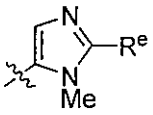
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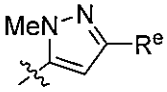
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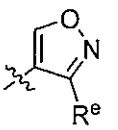
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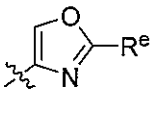
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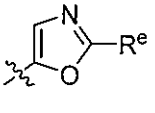
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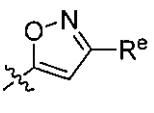
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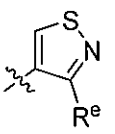
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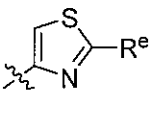


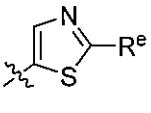
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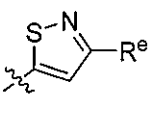


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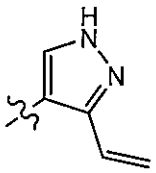
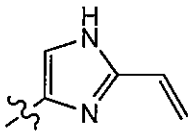
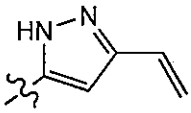
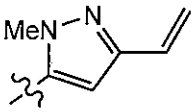
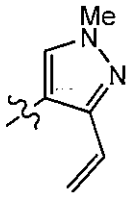




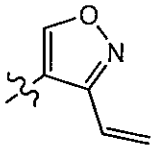
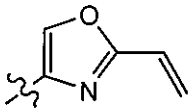
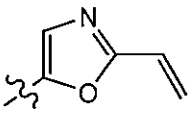
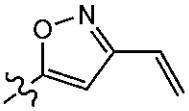
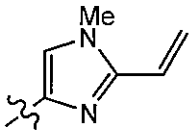




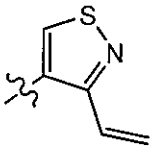
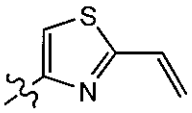
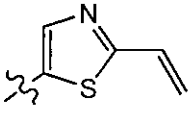
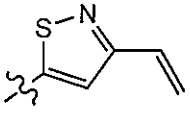
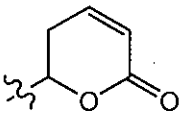
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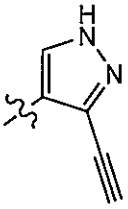
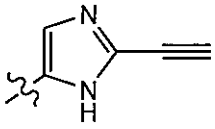
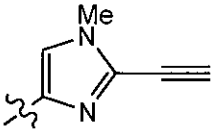
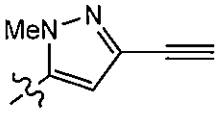
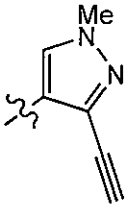
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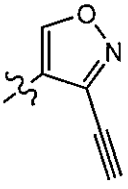
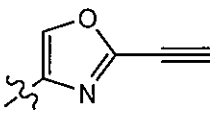
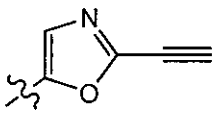
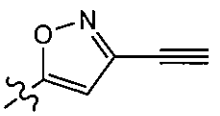
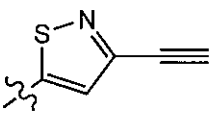
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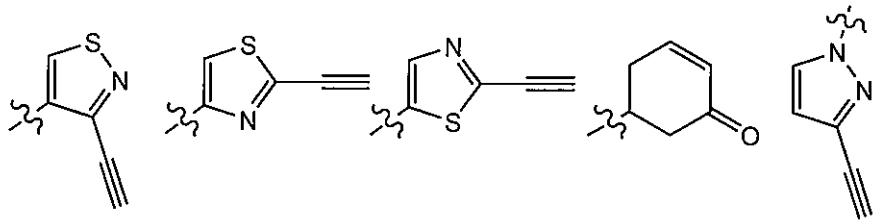
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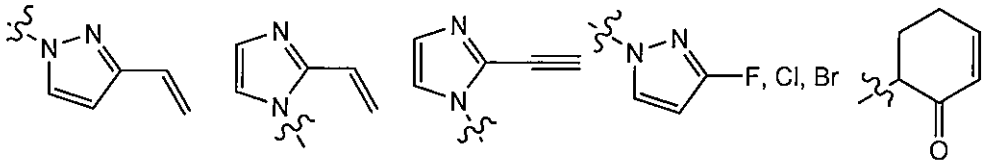
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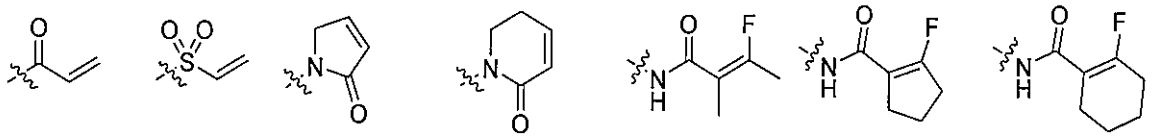
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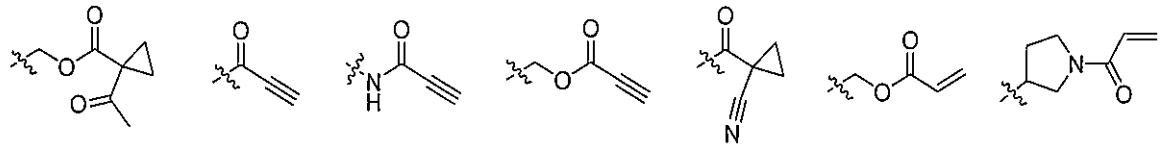
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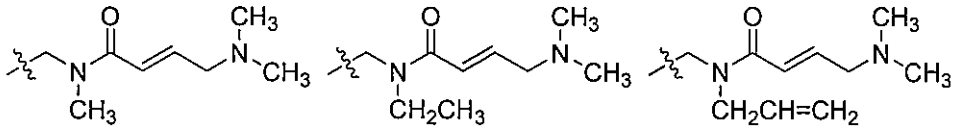
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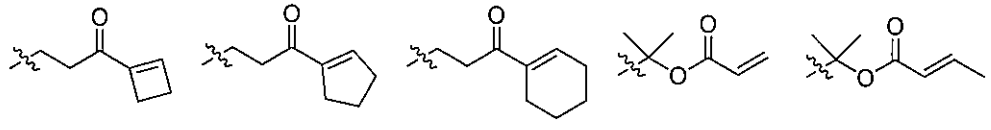
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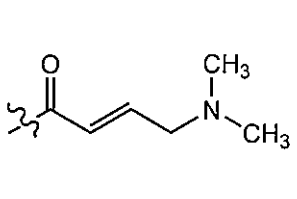
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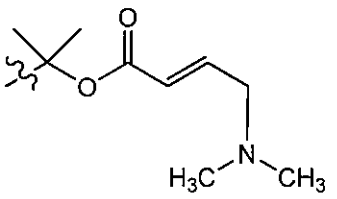
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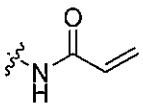
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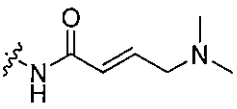
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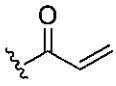
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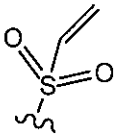
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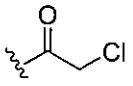
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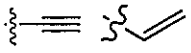
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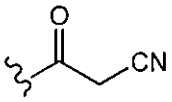
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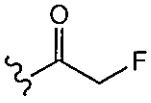
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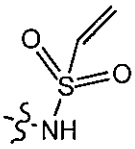
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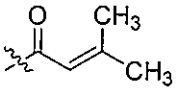
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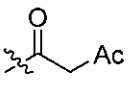
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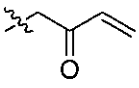
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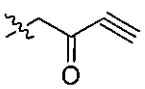
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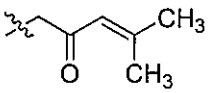
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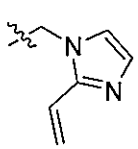
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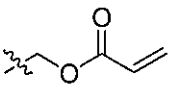
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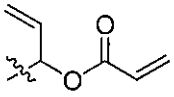
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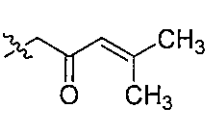
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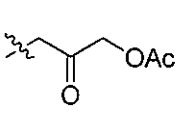
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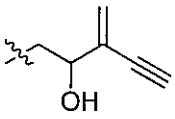
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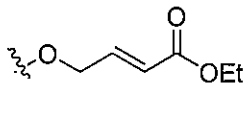
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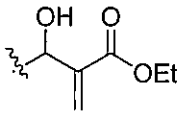
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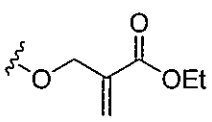
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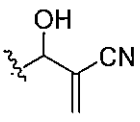
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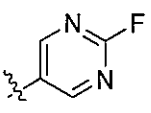
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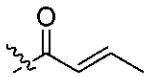
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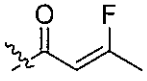


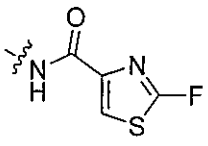
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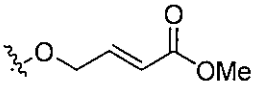


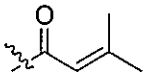
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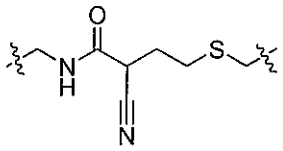




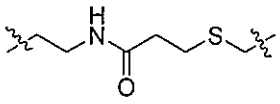
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wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

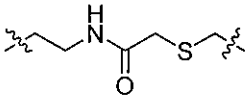
4. The conjugate of claim 1, wherein the modifier moiety taken together with the side chain Sulfur and methylene of the cysteine have a formula selected from the group consisting of



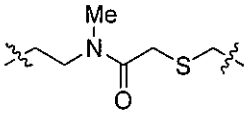
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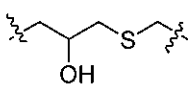
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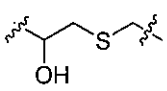
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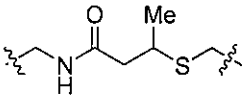
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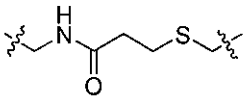
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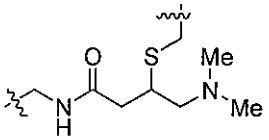
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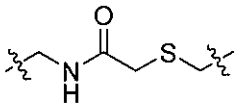
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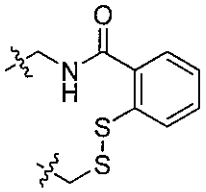
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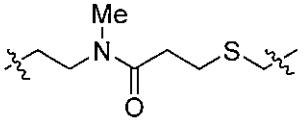
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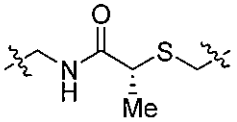
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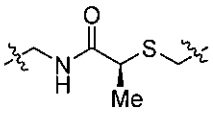
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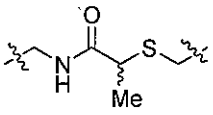
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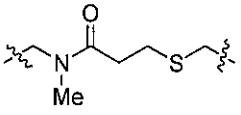
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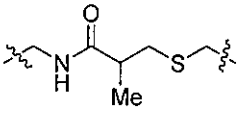
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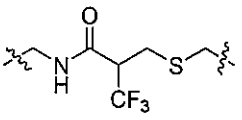
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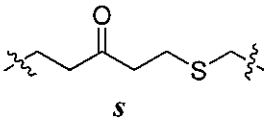
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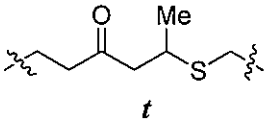
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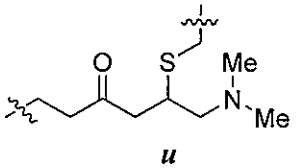
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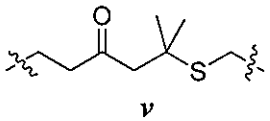
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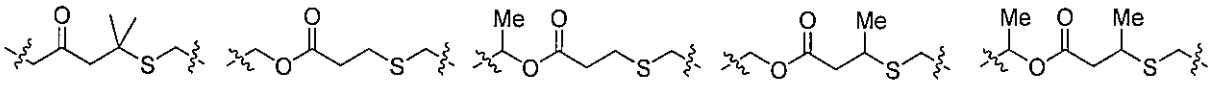
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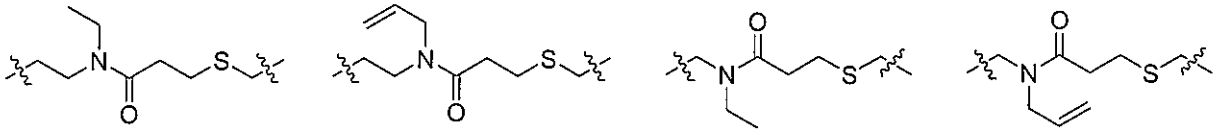
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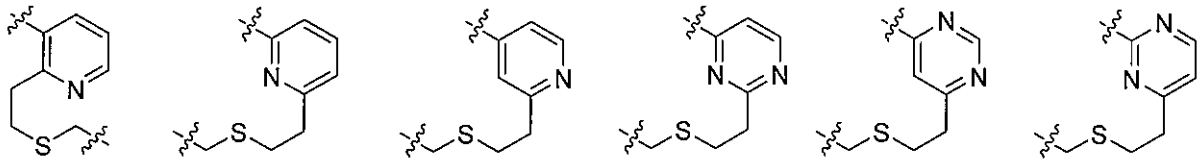
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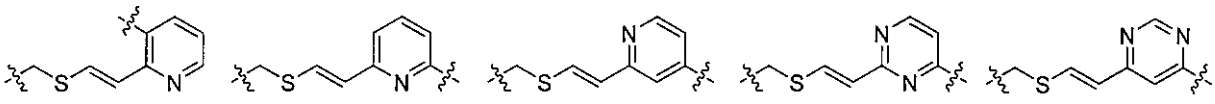
w *x* *y* *z* *aa*



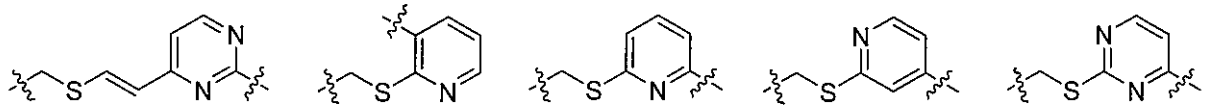
bb *cc* *dd* *ee*



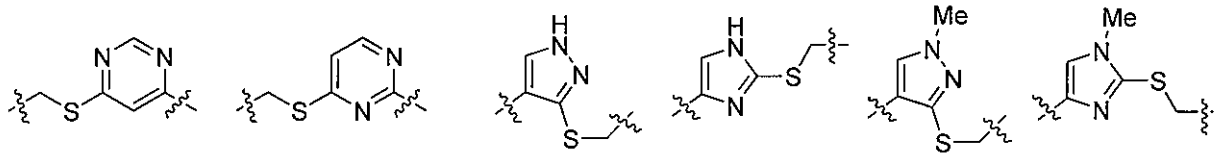
ff *gg* *hh* *ii* *jj* *kk*



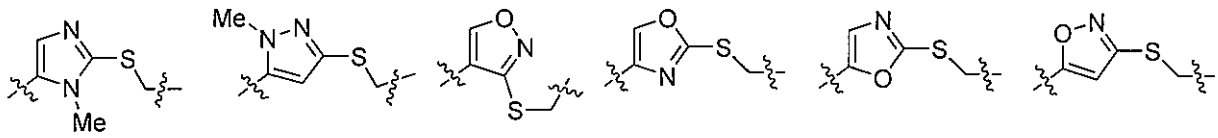
ll *mm* *nn* *oo* *pp*



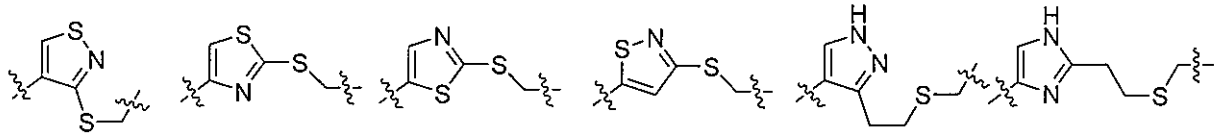
qq *rr* *ss* *tt* *uu*



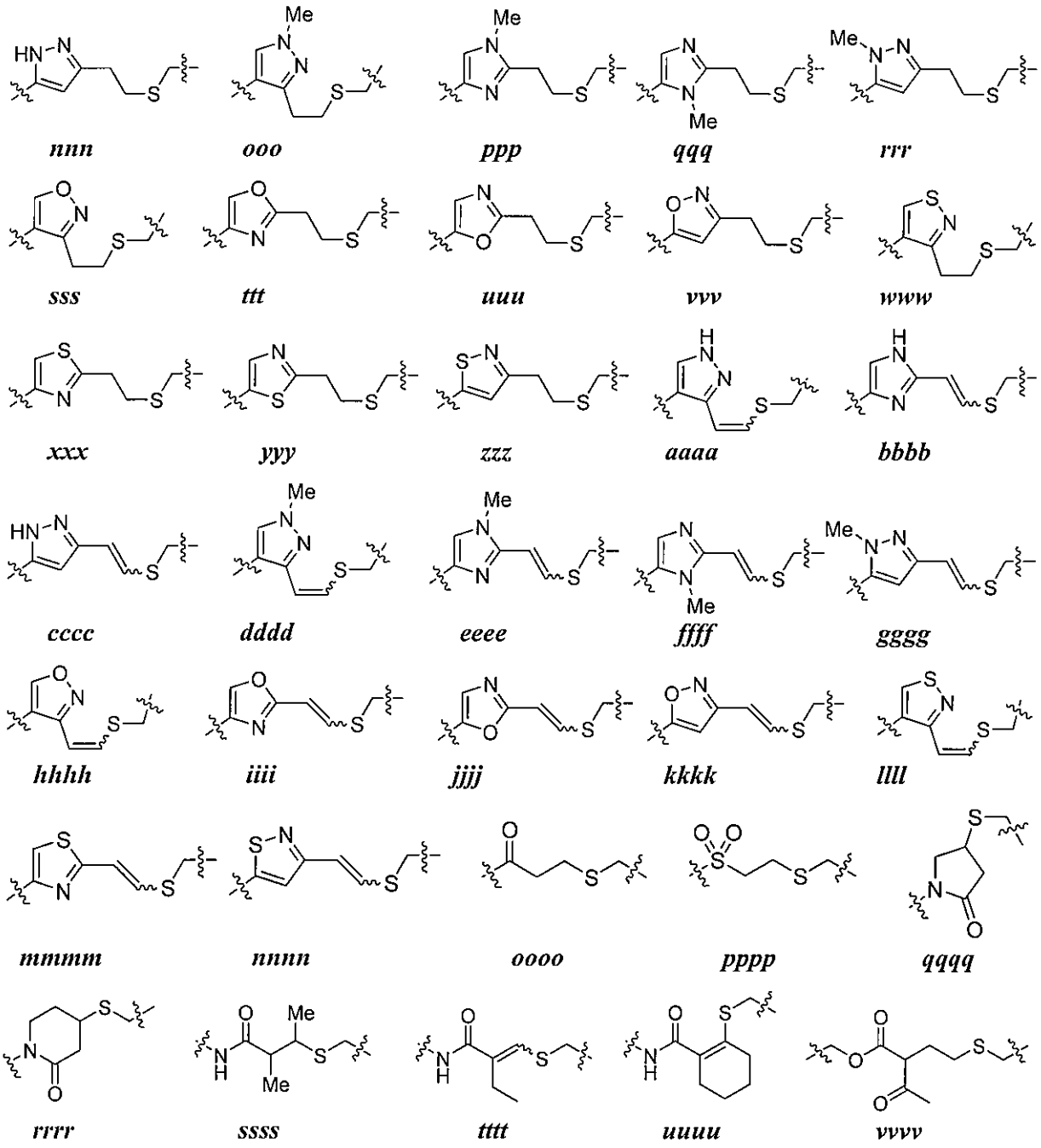
vv *ww* *xx* *yy* *zz* *aaa*

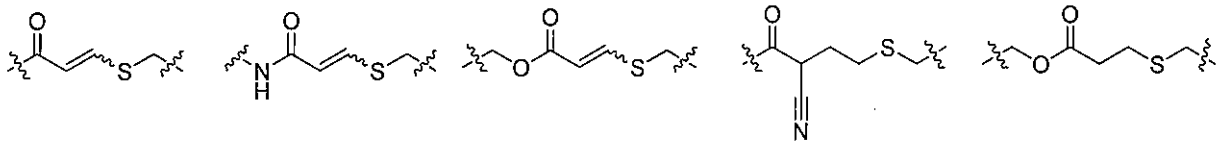


bbb *ccc* *ddd* *eee* *fff* *ggg*

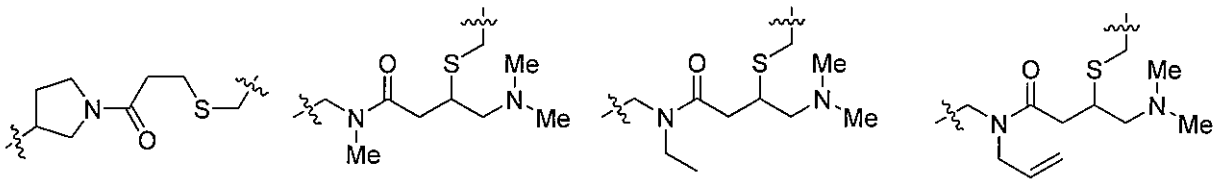


hhh *iii* *jjj* *kkk* *lll* *mmm*

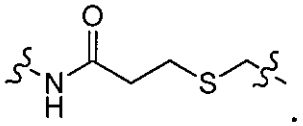

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wwww *xxxx* *yyyy* *zzzz* *aaaaa*



bbbbb ***ccccc*** ***ddddd*** ***eeeee***



and ***fffff.***

5. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS1, and is selected from the group consisting of JAK3, FGFR1, FGFR2, FGFR3, FGFR4, CKIT, CSFR1, PDGFR-A, FAK2, FLT3, FER, FES, CDKL1, CDKL4, FLT4, KDR, FLT1, PDGFR-B, and a portion of any one of the foregoing that comprises CYS1.

6. The conjugate of claim 5, wherein Prot comprises an amino acid sequence selected from the group consisting of RC*VHRDL, KC*IHRDL, NC*IHRDL, NC*IHRDV, NC*VHRDL, NC*VHRDI, SC*VHRDL, CC*IHRDL, or NC*IHRDI, wherein C* is CYS1.

7. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS5, and is selected from the group consisting of PFTAIRE1, JNK1, JNK2, JNK3 BMPR2, and a portion of any one of the foregoing that comprises CYS5.

8. The conjugate of claim 7, wherein Prot comprises an amino acid sequence selected from the group consisting of DLC*QYMD, NLC*QVIH, NLC*QVIQ, and SLC*KYLSL, wherein C* is CYS5.

9. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS6, and is selected from the group consisting of TNK1, YES, FGR, SRC, LIMK1, FGFR1, FGFR2, FGFR3, FGFR4, and a portion of any one of the foregoing that comprises CYS6.

10. The conjugate of claim 9, wherein Prot comprises an amino acid sequence selected from the group consisting of SGC*FGV, QGC*FGE, TGC*FGD, KGC*FGQ, and EGC*FGQ, wherein C* is CYS6.

11. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS7, and is selected from the group consisting of FAK, ALK1, ALK2, and a portion of any one of the foregoing that comprises CYS7.

12. The conjugate of claim 11, wherein Prot comprises an amino acid sequence selected from the group consisting of GRC*IGEGQFGD, VEC*VGKGRYG, and LEC*VGKGRYG, wherein C* is CYS7.

13. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS8, and is selected from the group consisting of ZAP70, CRIK, ERK3, CK1g1, CK1g2, CK1g3, and a portion of any one of the foregoing that comprises CYS8.

14. The conjugate of claim 13, wherein Prot comprises an amino acid sequence selected from the group consisting of GC*GNF, GC*GHF, and GC*GGN, wherein C* is CYS8.

15. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS9, and is ROR1or a portion thereof that comprises CYS9.

16. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS10, and is MELK or a portion thereof that comprises CYS10.

17. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS11, and is selected from the group consisting of c-KIT, FMS, RON, FLT3, FGR, and a portion of any one of the foregoing that comprises CYS11.

18. The conjugate of claim 17, wherein Prot comprises an amino acid sequence selected from the group consisting of YCC*YG, TMC*HG, and FMC*HG, wherein C* is CYS11.

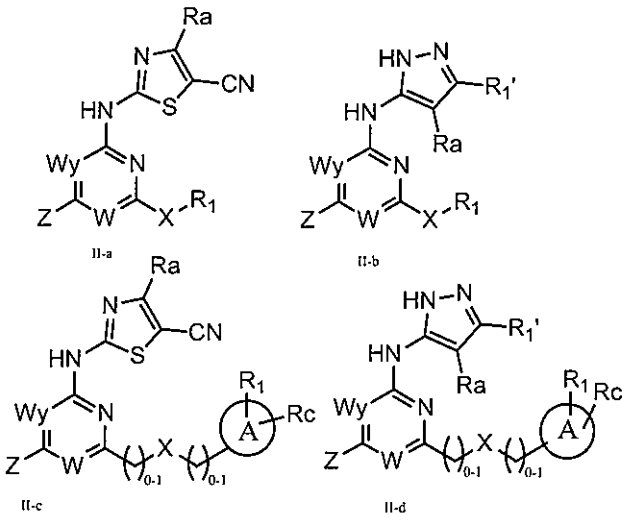
19. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS12, and is ALK or a portion thereof that comprises CYS12.

20. The conjugate of claim 19, wherein Prot comprises the amino acid sequence AARNCLLTC*PGPGRVAKIGD, wherein C* is CYS12.

21. The conjugate of any one of claims 1-4, wherein Prot is a kinase or portion of a kinase comprising CYS13, and is B-RAF or a portion thereof that comprises CYS13.

22. The conjugate of claim 21, wherein Prot comprises the amino acid sequence TKPQLAIVTQWC*EGSSLYHH, wherein C* is CYS13.

23. The protein kinase conjugate of claim 1, comprising a compound of formula II-a, II-b, II-c or II-d that is covalently and irreversibly bonded to the cysteine residue of Prot:



or a pharmaceutically acceptable salt thereof, wherein:

Wy is N or C-Rb;

W is N or CH;

X is NH, CH_2, O or S;

each of R^a R^b,and R^c are independently selected from R, OR, halogen, $-CF_3$, -CN, -C≡C-R, -NRxRy, or –C(O)NHRz;

each R, Rx and Ry is independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each Rz is independently hydrogen, aliphatic, or aryl;

Z is hydrogen or a solubilizing group;

Ring A is a 4-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring containing 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R_1 or R_1' is –L-Y, with the proviso that when R_1 is –L-Y, R_1' is R, OR, halogen, $-CF_3$, -CN, -C≡C-R or –C(O)NHR', and when R_1' is –L-Y, R_1 is R, OR, halogen, $-CF_3$, -CN, -C≡C-R or –C(O)NHR';

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene 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 hydrogen, nitrile, C_{1-6} aliphatic optionally substituted with one or more OH, NRxRy, 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

Rx and Ry are independently hydrogen, lower alkyl, lower haloalkyl, or lower cycloalkyl;

each R^e is independently selected from –Q-Z, OH, 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.