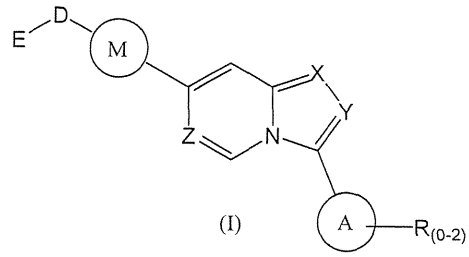
We claim:

1. A compound having a structure represented by the following formula (I):

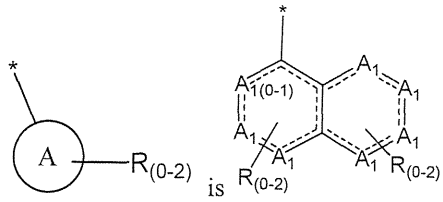



(I)

wherein:

X is N;

Y and Z are independently N or CH;




each $A_1$ is independently O, S, $CR_{1a}R_2$, or $NR_{1a}$;

R is selected from $CF_3$, halogen, CN, alkyl, aryl, heteroaryl, or $NR_1R_2$;

M is substituted or unsubstituted and is selected from aryl or heteroaryl;

D is selected from a bond, O, $CR_1R_2$, NH, $NR_1$ or $NR_1R_2$;

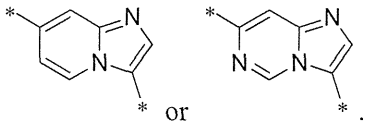
E is absent or selected from H, $CF_3$, halogen, CN, alkyl, aryl, heteroaryl, $C_3$-$C_{12}$ cycloalkyl, $C_3$-$C_{12}$ cycloheteroalkyl, $-(CH_2)_x-C_3$-$C_{12}$ cycloalkyl or $-(CH_2)_x-C_3$-$C_{12}$ cycloheteroalkyl;

$R_{1a}$ is absent or selected from H, alkyl, aryl, or heteraryl;

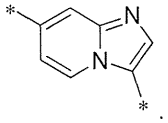
$R_1$ is selected from H, alkyl, aryl, or heteraryl; and

$R_2$ is selected from H, alkyl, aryl, heteroaryl, or $COR_1$, or $R_1$ and $R_2$ form a $C_3$-$C_{12}$ cycloalkyl or $C_3$-$C_{12}$ cycloheteroalkyl containing O, N and/or S; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein X, Y and Z are selected to form:

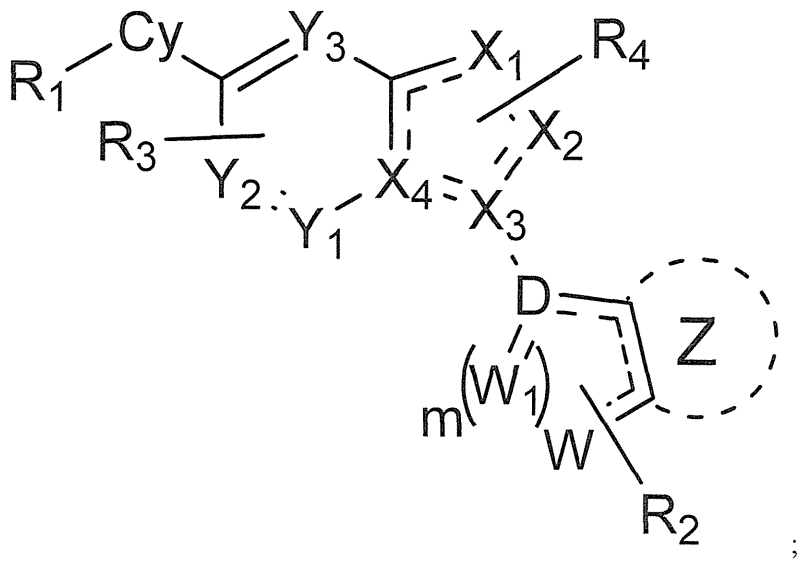
 or .

3. The compound of claim 1, wherein X, Y and Z are selected to form:

 .

4. The compound of claim 1, wherein M is optionally substituted with one or more R, and is selected from $C_3$-$C_{12}$ cycloalkyl, $C_3$-$C_{12}$ cycloalkenyl, aryl, heteroaryl, $C_3$-$C_{12}$

15. A compound having a structure represented by the following formula:




;

wherein:

$X_1$ is N;

$X_2$ is N or $CR_{1a}$;

$X_3$ is C;

$X_4$ is N;

$Y_1$ and $Y_3$ are $CR_{1a}$;

$Y_2$ is N or $CR_{1a}$

D is C or N;

W is N or O;

$W_1$ is N, O or C;

Cy is optionally substituted with one or more $R_1$, and is selected from $C_3$-$C_{12}$ cycloalkyl or $C_3$-$C_{12}$ cycloalkenyl or aryl or heteroaryl or $C_3$-$C_{12}$ heterocycloalkyl or $C_3$-$C_{12}$ heterocycloalkenyl or 3-8 membered ring comprising C, O, S, and/or N.

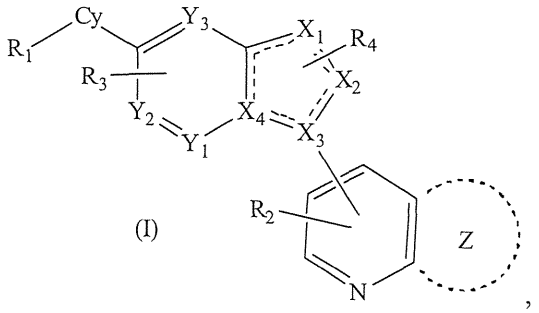
$R_{1a}$ is absent or selected from hydrogen, halogen, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}10}$ cycloalkyl, $OC_{1\text{-}10}$ alkyl (which may contain a $C_{3\text{-}8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), $NR_1C_{1\text{-}10}$ alkyl (which may contain a $C_{3\text{-}8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

$R_1$–$R_4$ are independently selected from hydrogen, halogen, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}10}$ cycloalkyl, $OC_{1\text{-}10}$ alkyl (which may contain a $C_{3\text{-}8}$ membered ring containing C, O, S or N, optionally

substituted with one or more $R^4$), $NR_1C_{1-10}$ alkyl (which may contain a $C_{3-8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

Z is optionally substituted with one or more $R_1$, and is selected from $C_3$-$C_{12}$ cycloalkyl or $C_3$-$C_{12}$ cycloalkenyl or aryl or heteroaryl or $C_3$-$C_{12}$ heterocycloalkyl or $C_3$-$C_{12}$ heterocycloalkenyl or 3-8 membered ring comprising C, O, S, and/or N.

16. A compound having a structure represented by the following formula:




(I)

,

wherein:

$X_1$ is N;

$X_2$is N or $CR_{1a}$;

$X_3$ is C;

$X_4$ is N;

$Y_1$ and $Y_3$ are $CR_{1a}$;

$Y_2$ is N or $CR_{1a}$;

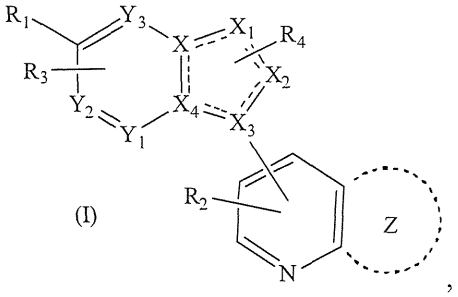
Cy is a bond, or forms a ring that is optionally substituted with one or more $R_1$, and is selected from $C_3$-$C_{12}$ cycloalkyl or $C_3$-$C_{12}$ cycloalkenyl or aryl or heteroaryl or $C_3$-$C_{12}$ heterocycloalkyl or $C_3$-$C_{12}$ heterocycloalkenyl or 3-8 membered ring comprising C, O, S, and/or N;

$R_{1a}$ is absent or selected from hydrogen, halogen, $C_{1-10}$ alkyl, $C_{3-10}$ cycloalkyl, $OC_{1-10}$ alkyl (which may contain a $C_{3-8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), $NR_1C_{1-10}$ alkyl (which may contain a $C_{3-8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

$R_1$–$R_4$ are independently selected from hydrogen, halogen, $C_{1-10}$ alkyl, $C_{3-10}$ cycloalkyl, $OC_{1-10}$ alkyl (which may contain a $C_{3-8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), $NR_1C_{1-10}$ alkyl (which may contain a $C_{3-8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

Z is optionally substituted with one or more $R_1$, and is selected from $C_3$-$C_{12}$ cycloalkyl or $C_3$-$C_{12}$ cycloalkenyl or aryl or heteroaryl or $C_3$-$C_{12}$ heterocycloalkyl or $C_3$-$C_{12}$ heterocycloalkenyl or 3-8 membered ring comprising C, O, S, and/or N.

17. A compound having a structure represented by the following formula:



(I)

,

wherein:

$X_1$ is N;

$X_2$ is N or $CR_{1a}$;

X is C;

$X_3$ is C or N;

$X_4$ is N;

$Y_1$ and $Y_3$ are $CR_{1a}$;

$Y_2$ is N or $CR_{1a}$;

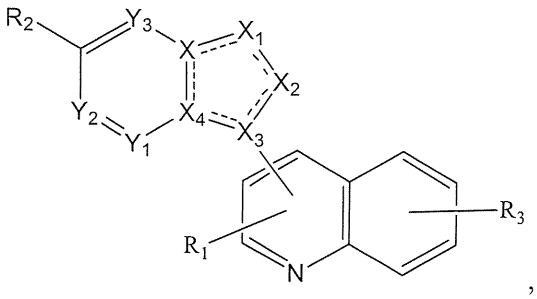
$R_{1a}$ is absent or selected from hydrogen, halogen, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}10}$ cycloalkyl, $OC_{1\text{-}10}$ alkyl (which may contain a $C_{3\text{-}8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

$R_1$ is independently selected from hydrogen, halogen, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}10}$ cycloalkyl, $OC_{1\text{-}10}$ alkyl (which may contain a $C_{3\text{-}8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

$R_2$-$R_4$ are absent or independently selected from hydrogen, halogen, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}10}$ cycloalkyl, $OC_{1\text{-}10}$ alkyl (which may contain a $C_{3\text{-}8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

Z is optionally substituted with one or more $R_1$, and is selected from $C_3$-$C_{12}$ cycloalkyl or $C_3$-$C_{12}$ cycloalkenyl or aryl or heteroaryl or $C_3$-$C_{12}$ heterocycloalkyl or $C_3$-$C_{12}$ heterocycloalkenyl or 3-8 membered ring comprising C, O, S, and/or N.

18. The compound of claim 17, wherein the compound is of the following formula:



,

wherein:

$X_1$ is N;

$X_2$ is N or $CR_{1a}$;

X is C;

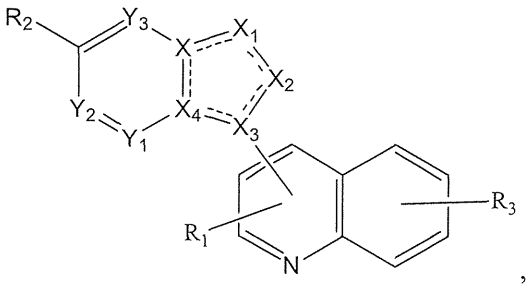
$X_3$ is C or N;

$X_4$ is N;

$Y_1$, $Y_2$, and $Y_3$ are $CR_{1a}$;

$R_1$-$R_4$ are absent or independently selected from hydrogen, halogen, $C_{1-10}$ alkyl, $C_{3-10}$ cycloalkyl, $OC_{1-10}$ alkyl (which may contain a $C_{3-8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$;

19. The compound of claim 17, wherein the compound is of the following formula:



wherein

(i) $X_2$ and $Y_2$ are $CR_{1a}$;

(ii) $X_2$ is N, $Y_2$ is N, and $X_3$ is C; or

(iii) $X_3$ is N, and $X_2$ and $Y_2$ are $CR_{1a}$;

$R_1$-$R_4$ are independently selected from hydrogen, halogen, $C_{1-10}$ alkyl, $C_{3-10}$ cycloalkyl, $OC_{1-10}$ alkyl (which may contain a $C_{3-8}$ membered ring containing C, O, S or N, optionally substituted with one or more $R^4$), CN or $CF_3$.