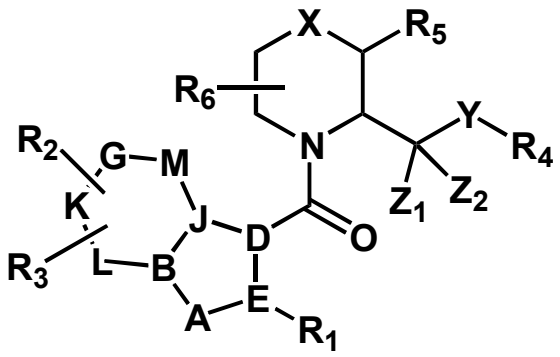
## CLAIMS

What is claimed is:

1. A compound of formula (I),




(I)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl;

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, $(C_{1-4})$alkyl, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{2-7})$cycloalkyl;

and wherein**:**

A-B-J-D-E is a five-member heteroaryl;

B-J-M-G-K-L is a six-member ring selected from the group consisting of aromatic, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

and wherein, optionally:

A is N; and/or,

B is C or N; and/or,

J is C or N; and/or,

D is C; and/or,

E is C; and/or,

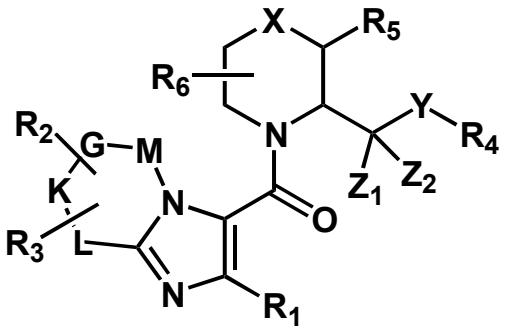
M is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, O; and/or,

G is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O; and/or,

K is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O; and/or,

L is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O.

2. A compound of formula **II**:




**(II)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, halogen, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, halogen, ($C_{1-$

$_3$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of ($C_{1-4}$)alkyl, ($C_{1-4}$) alkoxy, halogen, ($C_{1-3}$)fluoralkyl, ($C_{1-3}$)fluoroalkoxy, ($C_{3-7}$)cycloalkyl, and ($C_{3-7}$)heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

optionally wherein $R_5$ and $R_6$ connected as alkyl to form a ($C_{1-3}$)alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl;

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, ($C_{1-4}$)alkyl, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{2-7}$)cycloalkyl;

and wherein:

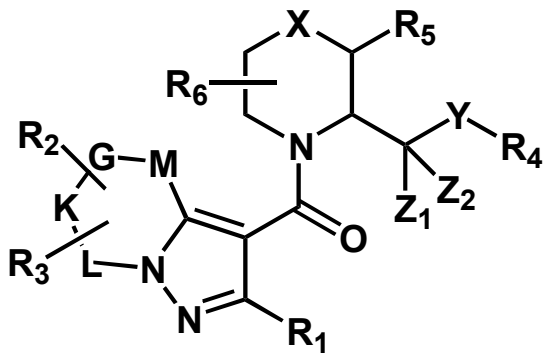
M is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, O; and/or,

G is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O; and/or,

K is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O; and/or,

L is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O.

3. A compound of formula **III**:




**(III)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by

two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl;

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, $(C_{1-4})$alkyl, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{2-7})$cycloalkyl;

and wherein:

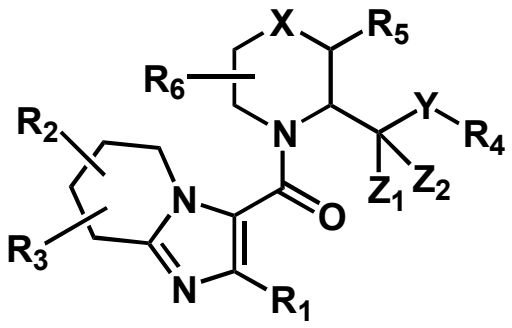
M is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, O; and/or,

G is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O; and/or,

K is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O; and/or,

L is selected from the group consisting of C, CH, $CR_2R_3$, $CR_2$, $CR_3$, and O.

4. A compound of formula **II-a**:




**(II-a)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent

is independently selected from the group consisting of ($C_{1-4}$)alkyl, ($C_{1-4}$) alkoxy, halogen, ($C_{1-3}$)fluoralkyl, ($C_{1-3}$)fluoroalkoxy, ($C_{3-7}$)cycloalkyl, and ($C_{3-7}$)heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

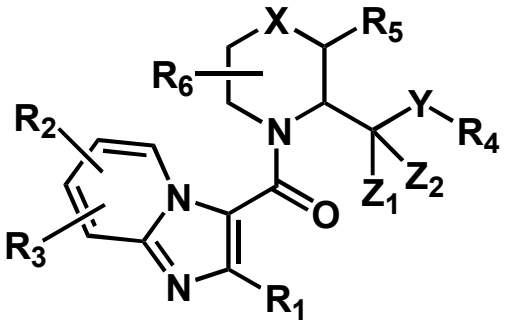
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a ($C_{1-3}$)alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl; and,

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, ($C_{1-4}$)alkyl, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{2-7}$)cycloalkyl.

5. A compound of formula **II-b**:




**(II-b)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl,

thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

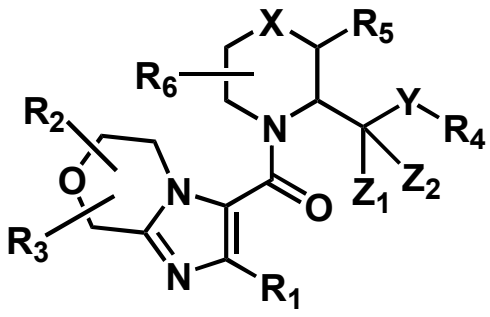
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl; and,

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, $(C_{1-4})$alkyl, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{2-7})$cycloalkyl.

6. A compound of formula **II-c**:




**(II-c)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic,

aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

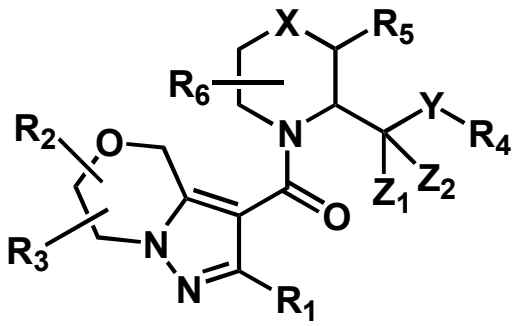
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl; and,

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, $(C_{1-4})$alkyl, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{2-7})$cycloalkyl.

7. A compound of formula **III-a**:




**(III-a)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said

heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

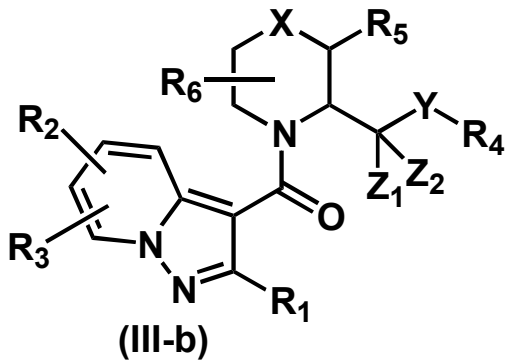
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl; and,

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, ($C_{1-4}$)alkyl, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{2-7}$)cycloalkyl.

8. A compound of formula **III-b**:




**(III-b)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, halogen, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, halogen, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by

two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

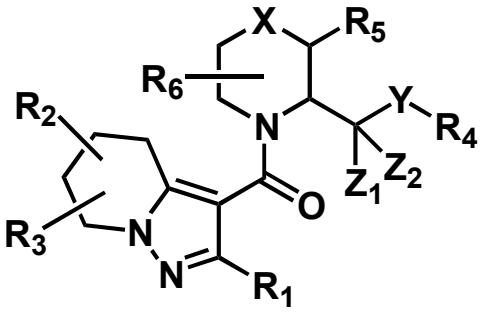
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl; and,

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, $(C_{1-4})$alkyl, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{2-7})$cycloalkyl.

9. A compound of formula **III-c**:




**(III-c)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl,

thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

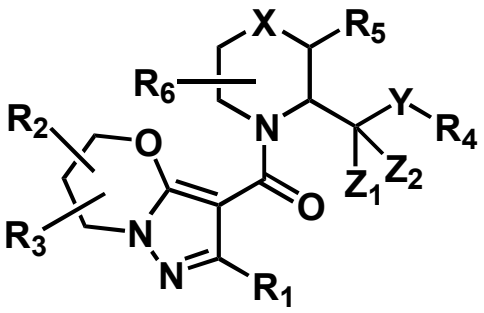
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl; and,

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, ($C_{1-4}$)alkyl, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{2-7}$)cycloalkyl.

10. A compound of formula **III-d**:




**(III-d)**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, halogen, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, halogen, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic,

aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

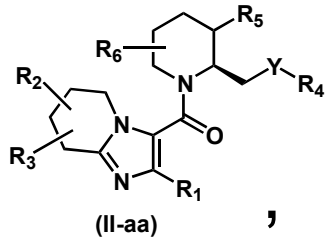
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure;

X is absent to provide a pyrrolidine ring, $CH_2$ to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the pyrrolidine ring is optionally in absolute (S)-configuration; and wherein the carbon atom at position 2 of the of the morpholine ring is optionally in absolute (R)-configuration;

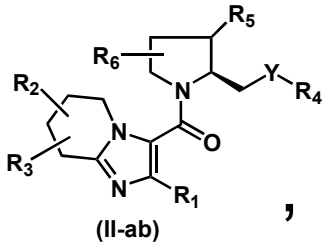
Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl; and,

$Z_1$ and $Z_2$ are each independently selected from the group consisting of H, F, $(C_{1-4})$alkyl, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{2-7})$cycloalkyl.

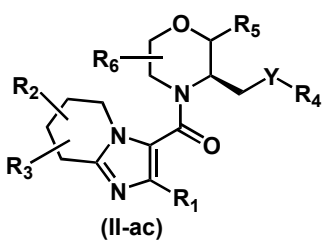
11. A compound of formula **II-aa**, **II-ab**, **II-ac, II-ba**, **II-bb**, **II-bc**, **II-ca**, **II-cb**, or **II-cc**:



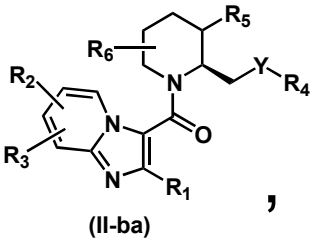
(II-aa) ,



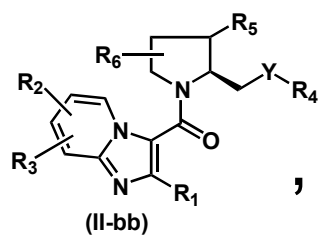
(II-ab) ,



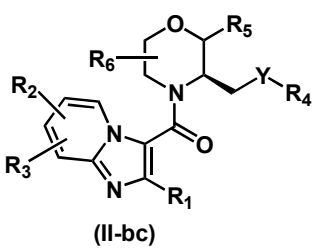
(II-ac)



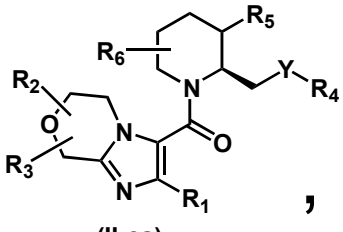
(II-ba) ,



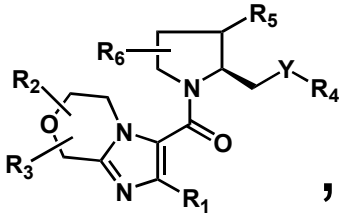
(II-bb) ,



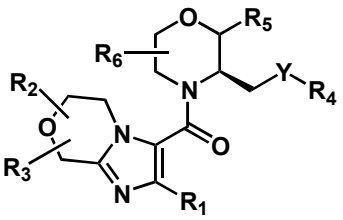
(II-bc)




(II-ca) ,




(II-cb) ,




(II-cc) ,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-3})$fluoroalkoxy, and $(C_{3-7})$cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$ alkoxy, halogen, $(C_{1-3})$fluoralkyl, $(C_{1-3})$fluoroalkoxy, $(C_{3-7})$cycloalkyl, and $(C_{3-7})$heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

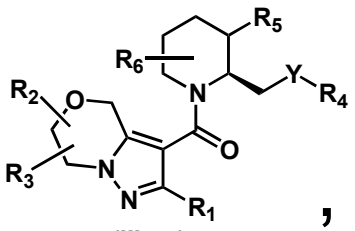
$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

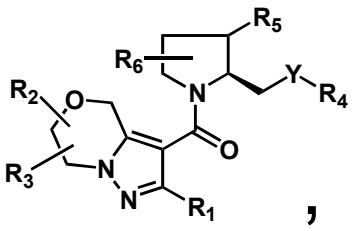
$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

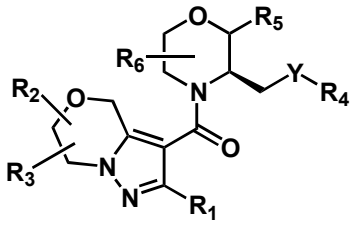
optionally wherein $R_5$ and $R_6$ connected as alkyl to form a $(C_{1-3})$alkyl bridge cyclic structure; and,

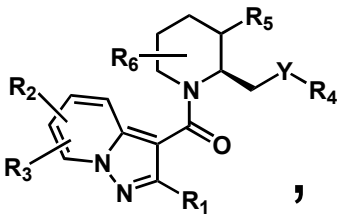
Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl.

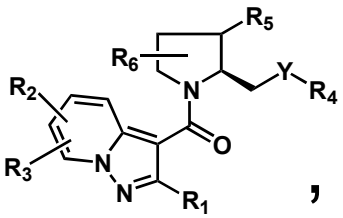
12. A compound of formula **III-aa**, **III-ab**, **III-ac, III-ba**, **III-bb**, **III-bc,** and **III-ca**, **III-cb**, or **III-cc**:

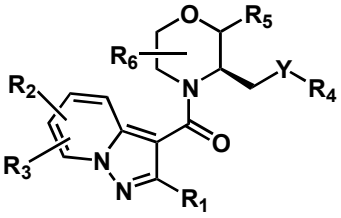

(III-aa)

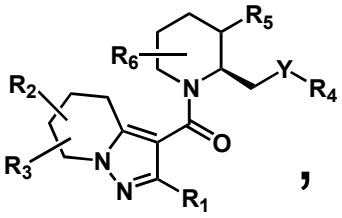

(III-ab)

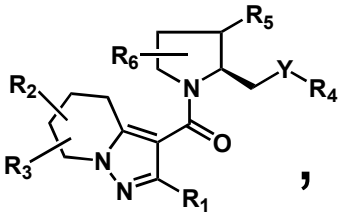

(III-ac)

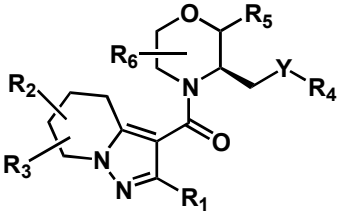

(III-ba)


(III-bb)


(III-bc)


(III-ca)


(III-cb)


(III-cc)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof;

wherein:

$R_1$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl, substituted aromatic, substituted aryl, substituted five or six member heteroaryl; optionally wherein said heteroaryl is selected from the group consisting of pyrrolyl, pyrazolyl, triazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_1$ substituent or di-substituted by two $R_1$ substituents, wherein each $R_1$ substituent is independently selected from the group consisting of $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, halogen, $(C_{1-3})$fluoroalkyl, $(C_{1-}$

$_{3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_2$ and $R_3$ are independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein each $R_2$ and $R_3$ is independently and optionally substituted at each substitutable position with up to three $R_2$-$R_3$ substituents, wherein each $R_2$-$R_3$ substituent is independently selected from the group consisting of H, halogen, alkyl, substituted alkyl, ($C_{1-4}$)alkyl, ($C_{1-4}$)alkoxy, halogen, ($C_{1-3}$)fluoroalkyl, ($C_{1-3}$)fluoroalkoxy, and ($C_{3-7}$)cycloalkyl; wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

$R_4$ is selected from the group consisting of aromatic, aryl, five or six member heteroaryl; substituted aromatic, substituted aryl, and substituted five or six member heteroaryl; wherein said aromatic, aryl or heteroaryl is unsubstituted, mono-substituted by one $R_4$ substituent, di-substituted by two $R_4$ substituents, or tri-substituted by three $R_4$ substituents, wherein each $R_4$ substituent is independently selected from the group consisting of ($C_{1-4}$)alkyl, ($C_{1-4}$) alkoxy, halogen, ($C_{1-3}$)fluoralkyl, ($C_{1-3}$)fluoroalkoxy, ($C_{3-7}$)cycloalkyl, and ($C_{3-7}$)heterocycloalkyl; and wherein the halogen is optionally selected from the group consisting of F, Cl, Br, and I;

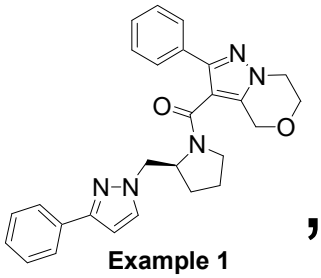
$R_5$ is selected from the group consisting of $CH_3$, alkyl, and substituted alkyl;

$R_6$ is selected from the group consisting of H, halogen, alkyl, and substituted alkyl, wherein said halogen is selected from the group consisting of F, Cl, Br, and I;

optionally wherein $R_5$ and $R_6$ connected as alkyl to form a ($C_{1-3}$)alkyl bridge cyclic structure; and,

Y is absent or selected from the group consisting of NH, O, $CH_2OR_4$, $CH_2$, and $NR_4R_7$ wherein $R_7$ is H or alkyl.

13. A compound selected from the group consisting of: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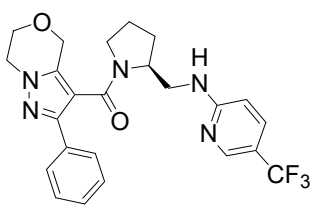
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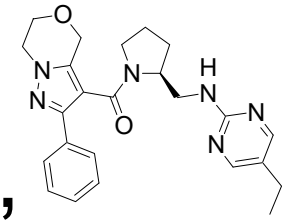
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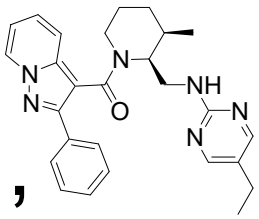
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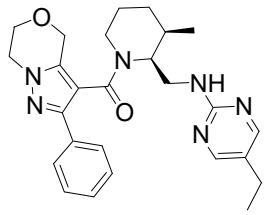
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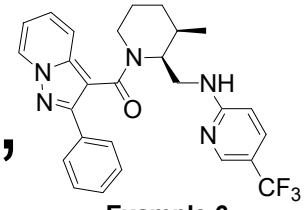
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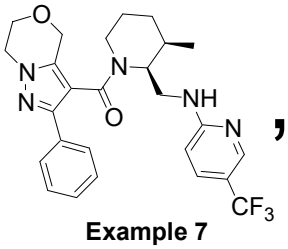
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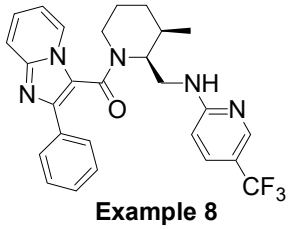
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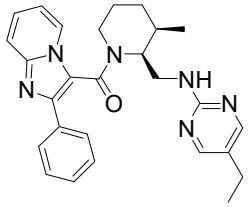
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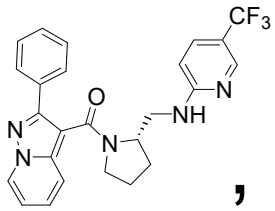
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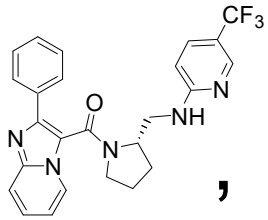
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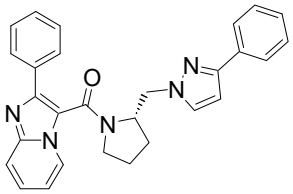
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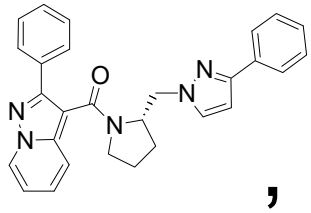
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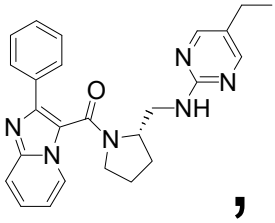
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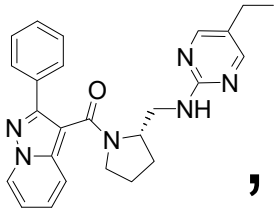
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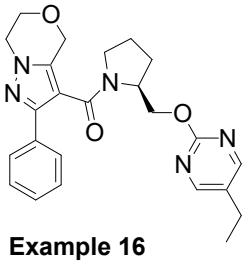
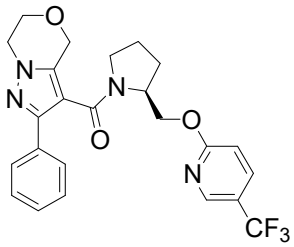

Example 16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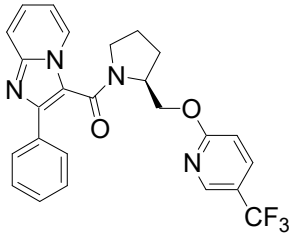
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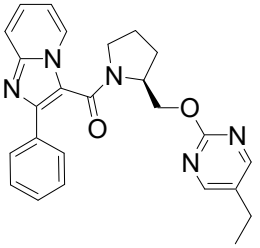
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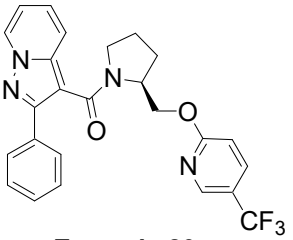
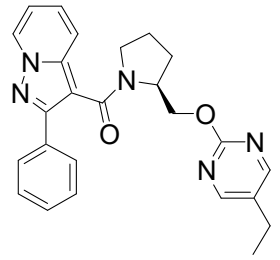

Example 20 and,



**Example 21**

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

14. A composition comprising a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof according to any preceding claim.

15. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, of any one of claims 1-13; and at least one pharmaceutically acceptable excipient, carrier, adjuvant, or vehicle.

16. The pharmaceutical composition of claim 15 comprising a therapeutically effective amount of the compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

17. The pharmaceutical composition according to claim 14, wherein said composition further comprises at least one second therapeutic agent.

18. A composition comprising a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, of any one of claims 1-13, for use in the prevention or treatment of a condition selected from the group consisting of a central nervous system (CNS) disorder, substance addiction, dependence, panic, anxiety, depression, posttraumatic stress disorder (PTSD), neurodegeneration, autism, schizophrenia, and Alzheimer disease (AD) in a subject in need thereof.

19. The composition for use of claim 18 wherein the composition comprises a therapeutically effective amount of the compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

20. The composition for use of claim 18 or 19 wherein the composition a pharmaceutically acceptable salt or isotope of the compound.

21. The composition for use of claim 18 or 19 wherein the composition comprises an unlabeled form of the compound or an isotopically labeled form of the compound in which the compound has a structure

depicted by the formula wherein one or more atoms are replaced by an atom having a selected atomic mass or mass number.

22. Use of a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, of any one of claims 1-13 in the preparation of a medicament for preventing and/or treating a condition selected from the group consisting of a central nervous system (CNS) disorder, substance addiction, dependence, panic, anxiety, depression, posttraumatic stress disorder (PTSD), neurodegeneration, autism, schizophrenia, and Alzheimer disease (AD) in a subject in need thereof.

23. The use of claim 22 wherein the composition comprises a therapeutically effective amount of the compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

24. The use of claim 22 or 23 wherein the composition a pharmaceutically acceptable salt or isotope of the compound.

25. The use of any one of claims 22-24 wherein the composition comprises an unlabeled form of the compound or an isotopically labeled form of the compound in which the compound has a structure depicted by the formula wherein one or more atoms are replaced by an atom having a selected atomic mass or mass number.

26. A method for preparing a compound, the method comprising a reaction selected from the group consisting of:

reacting Intermediate A with Intermediate F to produce a compound of Example 1;

reacting Intermediate A with Intermediate B to produce a compound of Example 2;

reacting Intermediate A with Intermediate C to produce a compound of Example 3;

reacting Intermediate J with Intermediate D to produce a compound of Example 4;

reacting Intermediate A with Intermediate D to produce a compound of Example 5;

reacting Intermediate J with Intermediate E to produce a compound of Example 6;

reacting Intermediate A with Intermediate E to produce a compound of Example 7;

reacting Intermediate I with Intermediate E to produce a compound of Example 8;

reacting Intermediate I with Intermediate D to produce a compound of Example 9;

reacting Intermediate J with Intermediate B to produce a compound of Example 10;

reacting Intermediate I with Intermediate B to produce a compound of Example 11;

reacting Intermediate I with Intermediate F to produce a compound of Example 12;

reacting Intermediate J with Intermediate F to produce a compound of Example 13;

reacting Intermediate I with Intermediate C to produce a compound of Example 14;

reacting Intermediate J with Intermediate C to produce a compound of Example 15;

reacting Intermediate A with Intermediate G to produce a compound of Example 16;

reacting Intermediate A with Intermediate H to produce a compound of Example 17;

reacting Intermediate I with Intermediate H to produce a compound of Example 18;

reacting Intermediate I with Intermediate G to produce a compound of Example 19;

reacting Intermediate J with Intermediate H to produce a compound of Example 20; and,

reacting Intermediate J with Intermediate G to produce a compound of Example 21.

27. A compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, of any one of claims 1-13, for use as a medicament.