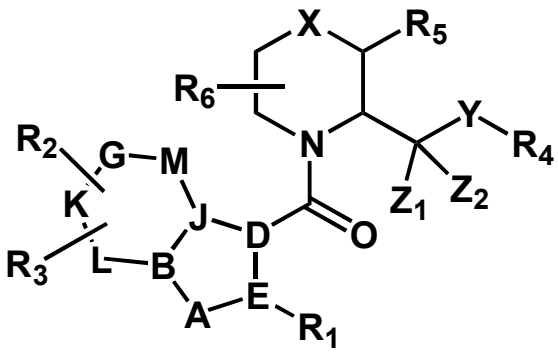
CLAIMS

What is claimed is:

1. A compound of formula (I),



(I)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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, (C_{1-4})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, (C_{1-4})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 H, CH_3, (C_{1-4})alkyl, and substituted alkyl when X is absent to provide a pyrrolidine ring; or R_5 is selected from the group consisting of CH_3, (C_{1-4})alkyl, and substituted alkyl when X is CH_2 to provide a piperidine ring, or R_5 is selected from the group consisting of CH_3, (C_{1-4})alkyl, and substituted alkyl when X is 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;

R_6 is selected from the group consisting of H, halogen, (C_{1-4})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, CH2 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_2O~~R_4~~, CH_2, and NR_4R_7 wherein R_7 is H or (C_{1-4})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~~ and 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,

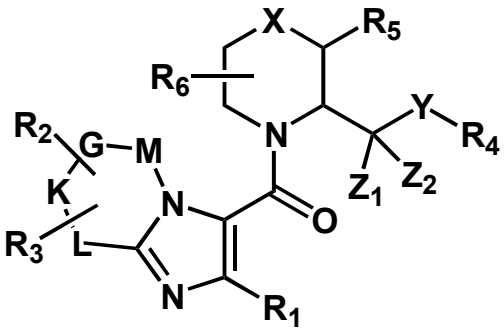
M is selected from the group consisting of C, CH, CR_2R_3, CR_2, CR_3, O; and/or,

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 according to claim 1, wherein the compound is of formula **II**:



(II)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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:

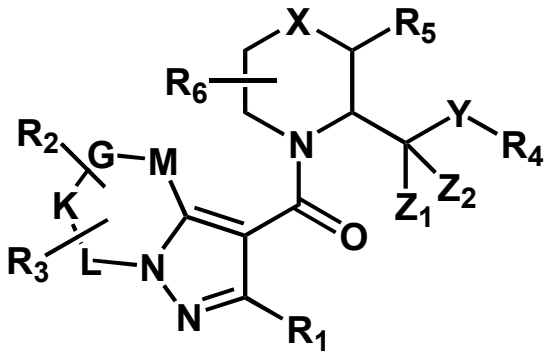
M is selected from the group consisting of C, CH, CR_2R_3, CR_2, CR_3, O; and/or,

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 according to claim 1, wherein the compound is of formula **III**:



(III)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, or combination thereof.;

wherein:

R_4 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_2R_3 substituents, wherein each R_2R_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:~~

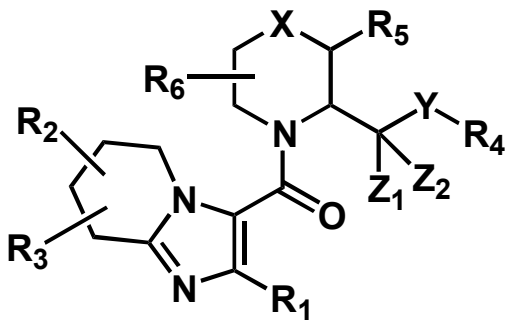
~~M is selected from the group consisting of C, CH, CR_2R_3, CR_2, CR_3, O; and/or,~~

~~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 according to claim 1, wherein the compound is of formula **II-a**:



(II-a)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_4 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_2R_3 substituents, wherein each R_2R_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;

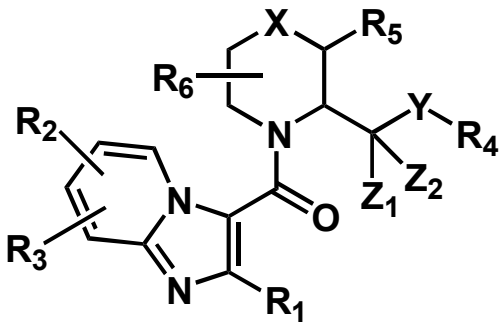
optionally wherein R_5 and R_6 connected as alkyl to form a (C_{1-3})alkyl bridge cyclic structure;

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 according to claim 1, wherein the compound is of formula **II-b**:



(II-b)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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;~~

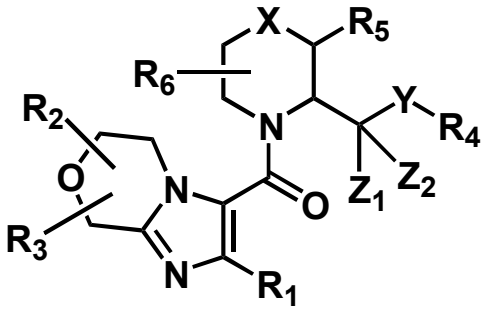
~~optionally wherein R_5 and R_6 connected as alkyl to form a (C_{1-3})alkyl bridge cyclic structure;~~

~~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 according to claim 1, wherein the compound is of formula **II-c**:



(II-c)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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;~~

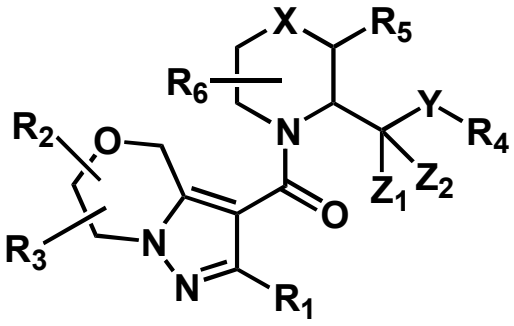
optionally wherein R_5 and R_6 connected as alkyl to form a (C_{1-3})alkyl bridge cyclic structure;

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 according to claim 1, wherein the compound is of formula **III-a**:



(III-a)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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;~~

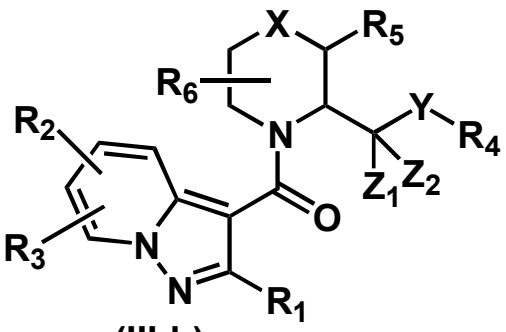
~~optionally wherein R_5 and R_6 connected as alkyl to form a (C_{1-3})alkyl bridge cyclic structure;~~

~~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 according to claim 1, wherein the compound is of formula **III-b**:



(III-b)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_4 substituent or di-substituted by two 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})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_2R_3 substituents, wherein each R_2R_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;

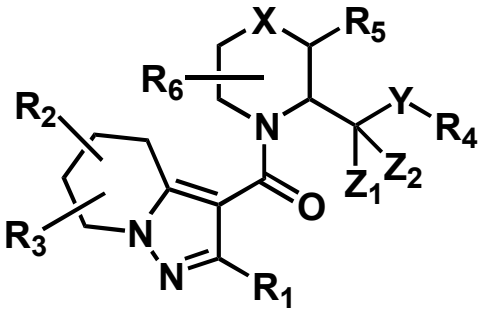
optionally wherein R_5 and R_6 connected as alkyl to form a (C_{1-3})alkyl bridge cyclic structure;

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 according to claim 1, wherein the compound is of formula **III-c**:



(III-c)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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;

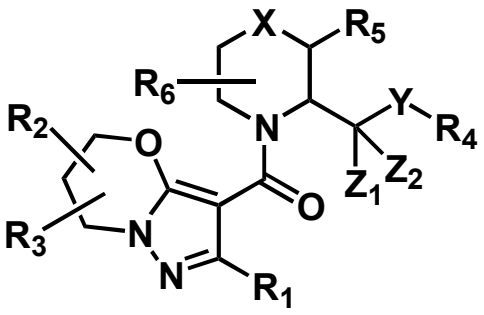
X is absent to provide a pyrrolidine ring, CH_2 to provide a piperidine ring, or O to provide a morpholine ring; wherein the carbon atom at position 2 of the of the piperidine ring or the

~~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 according to claim 1, wherein the compound is of formula **III-d**:



(III-d)

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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;~~

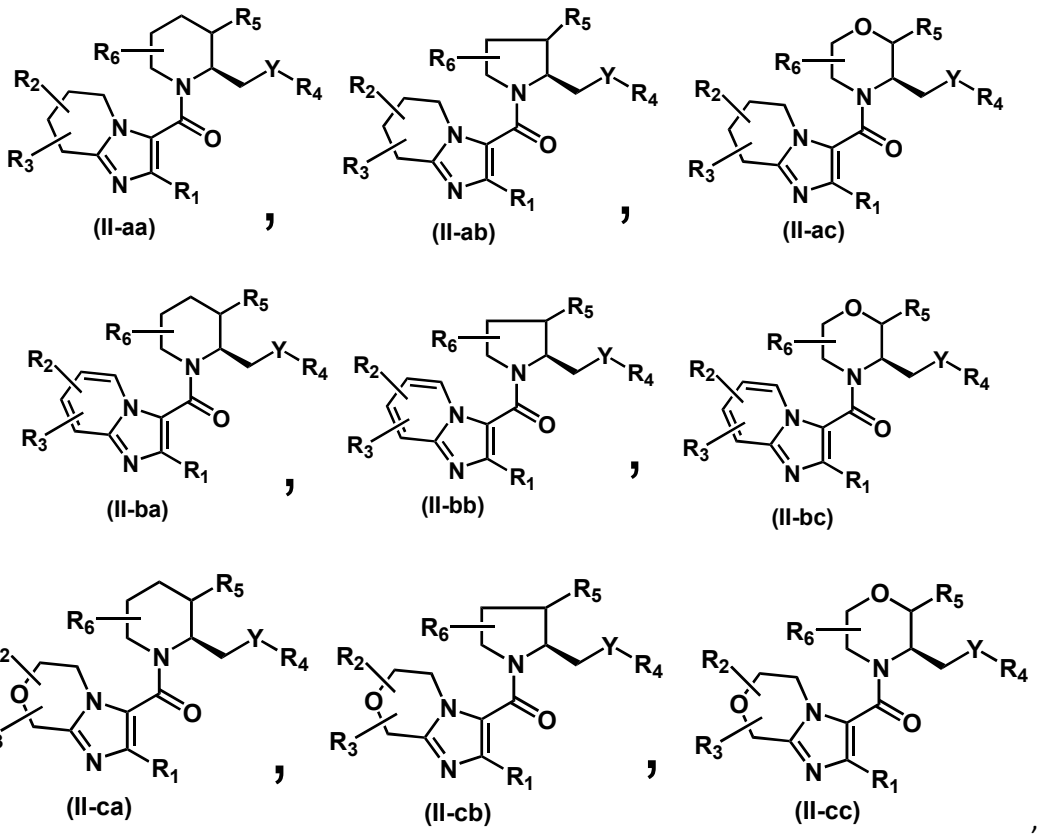
~~optionally wherein R_5 and R_6 connected as alkyl to form a (C_{1-3})alkyl bridge cyclic structure;~~

~~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 according to claim 1, wherein the compound is of formula **II-aa**, **II-ab**, **II-ac**, **II-ba**, **II-bb**, **II-bc**, **II-ca**, **II-cb**, or **II-cc**:



or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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;~~

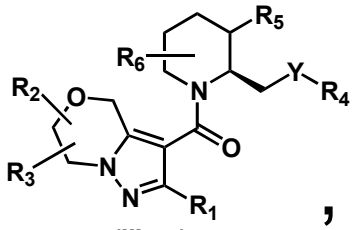
~~R_5 is selected from the group consisting of CH_3, alkyl, and substituted alkyl;~~

~~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;~~

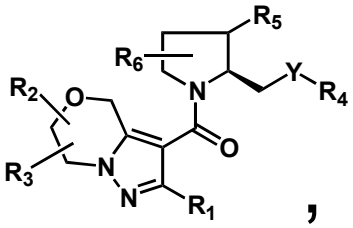
~~optionally wherein R_5 and R_6 connected as alkyl to form a (C_{1-3})alkyl bridge cyclic structure; and,~~

~~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.~~

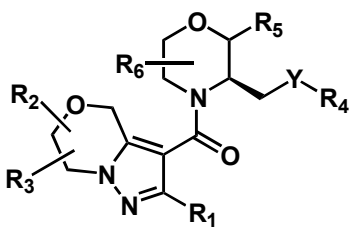
12. A compound according to claim 1, wherein the compound is of formula **III-aa**, **III-ab**, **III-ac,** **III-ba**, **III-bb**, **III-bc,** and **III-ca**, **III-cb**, or **III-cc**:



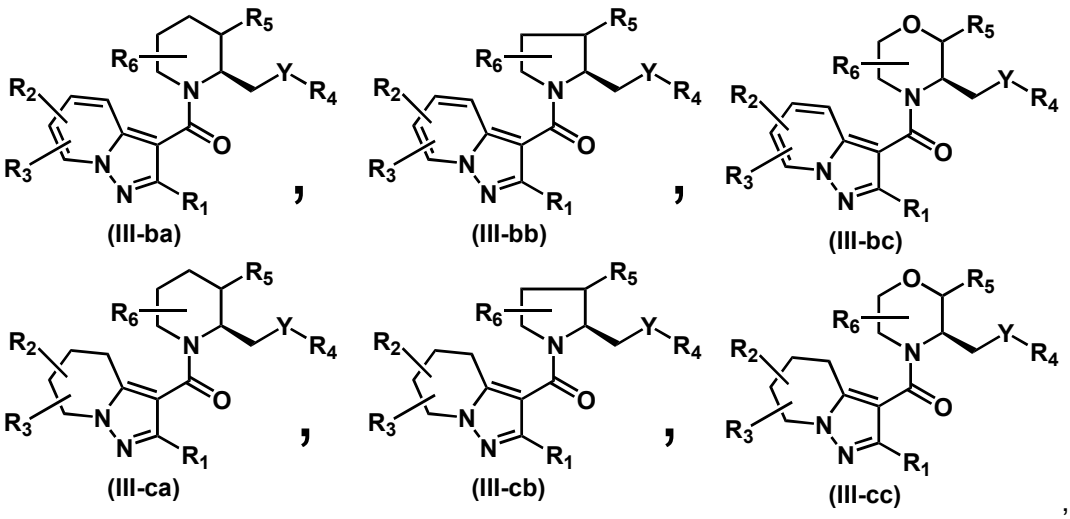
(III-aa) ,



(III-ab) ,



(III-ac) ,



or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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_2R_3 substituents, wherein each R_2R_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;~~

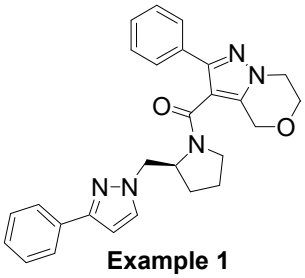
~~R_5 is selected from the group consisting of CH_3, alkyl, and substituted alkyl;~~

~~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 according to claim 1, wherein the compound is selected from the group consisting of:



Example 1

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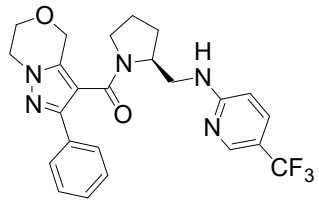

Example 2

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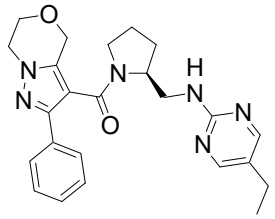

Example 3

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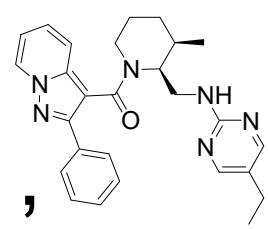
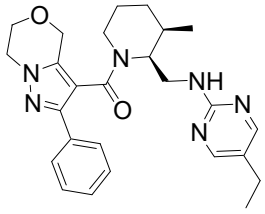


Example 4



Example 5

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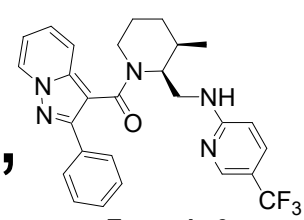

Example 6

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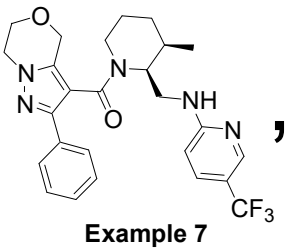

Example 7

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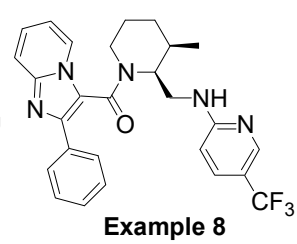
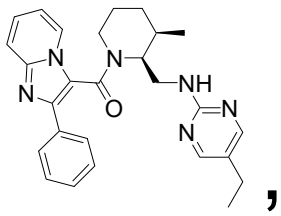
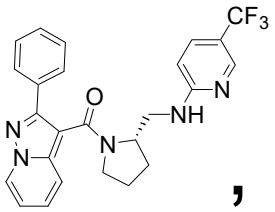


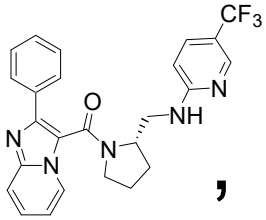
Example 8



Example 9 ,



Example 10 ,



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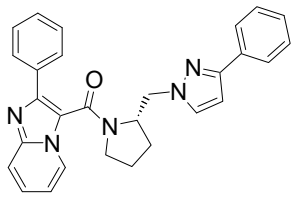
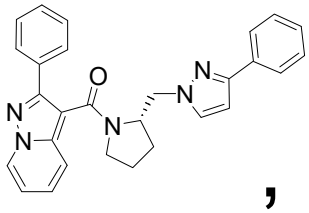


Example 12



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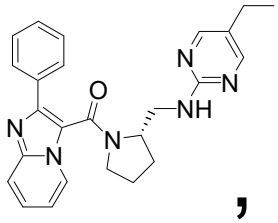

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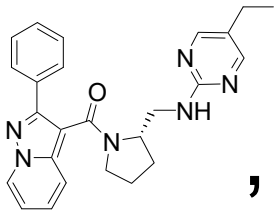

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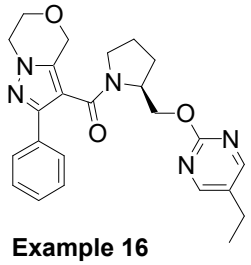
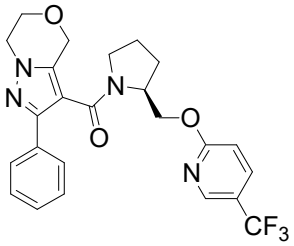


Example 16



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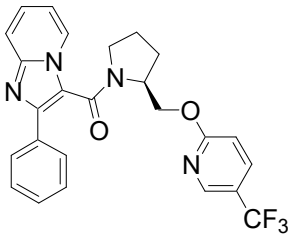

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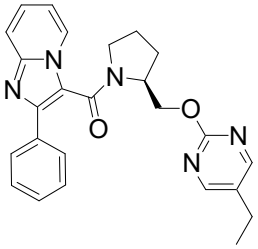

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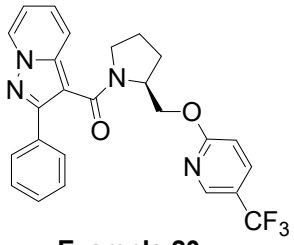
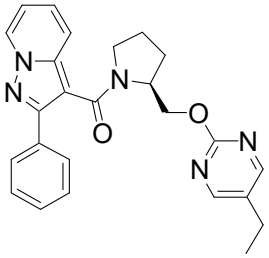


Example 20

and,



Example 21

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, or combination thereof.

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

15. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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 with respect to a stereogenic center, or combination thereof; optionally wherein said composition further comprises at least one second therapeutic agent.

~~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~~17. Use of a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, 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~~18. The use of claim ~~22~~ 17 wherein:

the ~~composition~~ medicament comprises a therapeutically effective amount of the compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, or combination thereof;

the composition comprises a pharmaceutically acceptable salt or isotope of the compound and/or

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.

~~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~~19. 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;~~

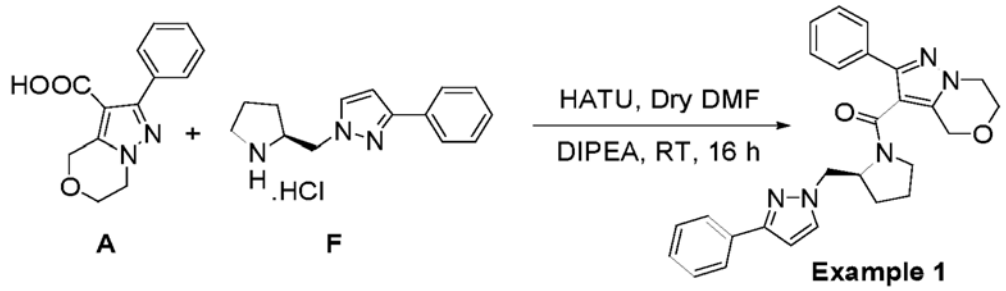
~~reacting Intermediate A with Intermediate H to produce a compound of Example 17;~~

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

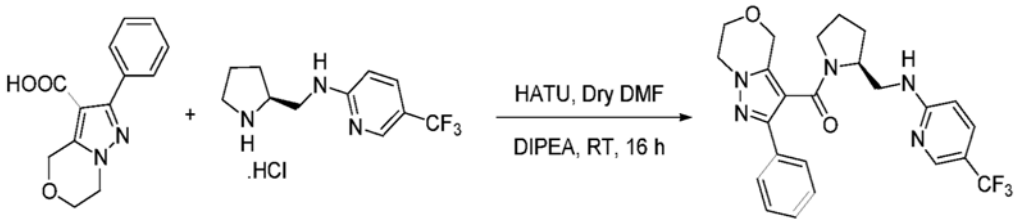
~~reacting Intermediate I with Intermediate G to produce a compound of Example 19;~~

~~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.~~



Example 1 ;



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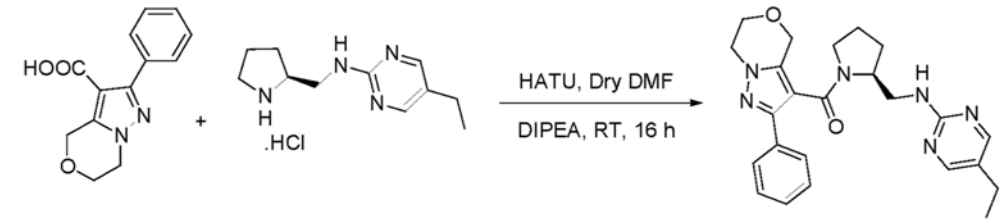

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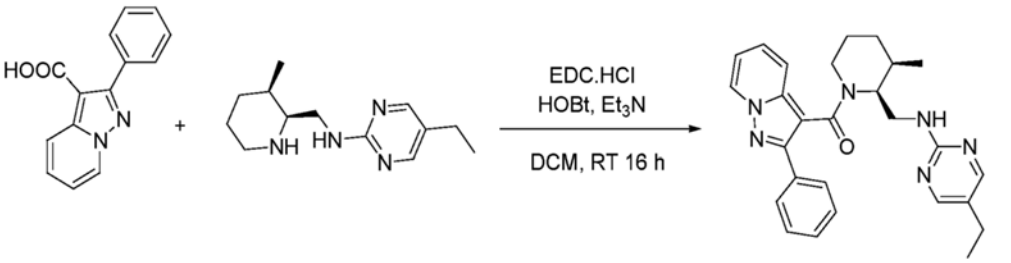
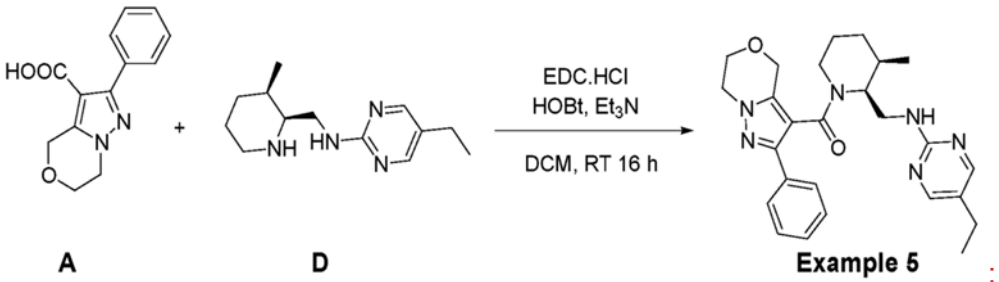


Example 4 ;



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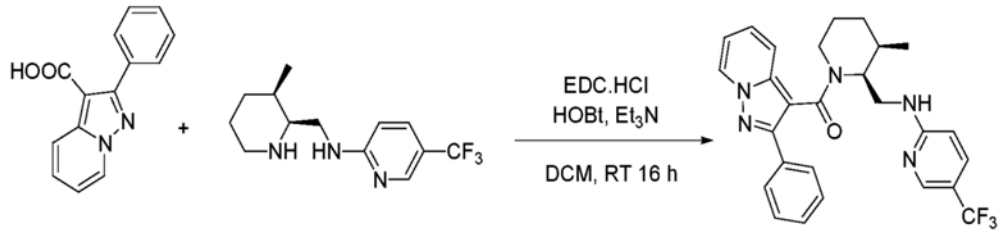
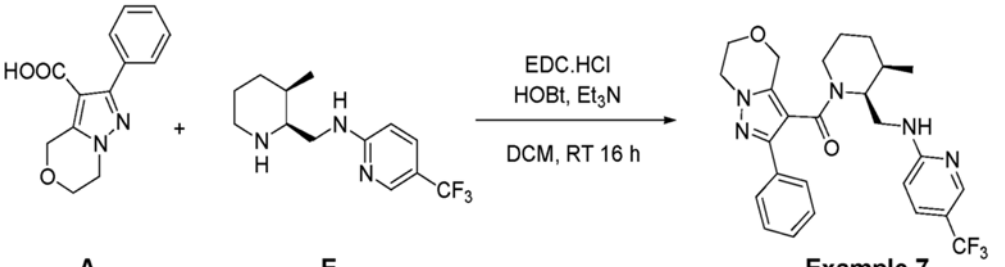
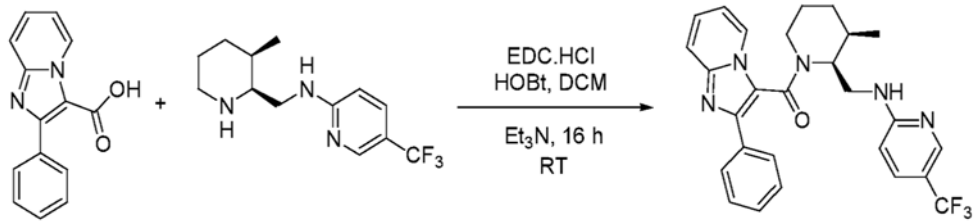


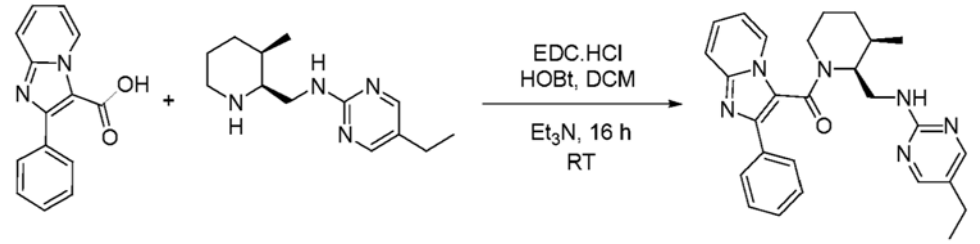
J E **Example 6**



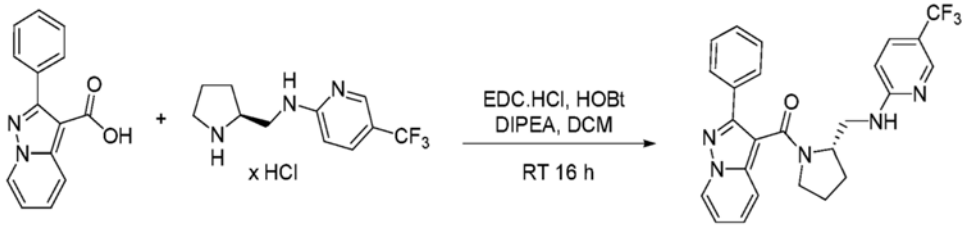
A E **Example 7**



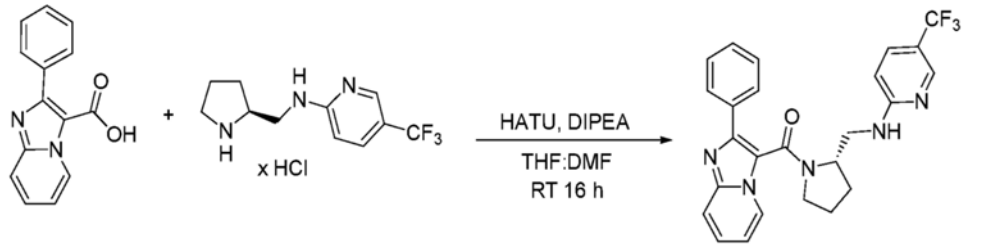
I E **Example 8**



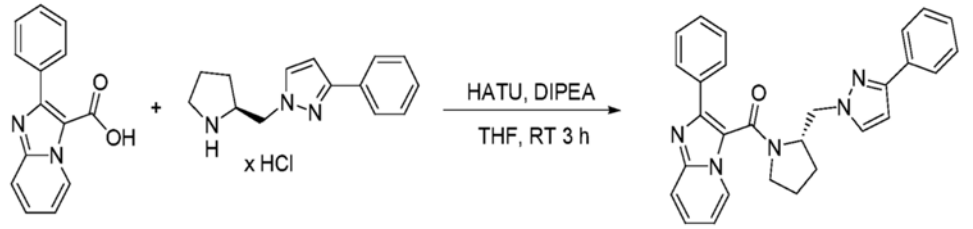
I D **Example 9**



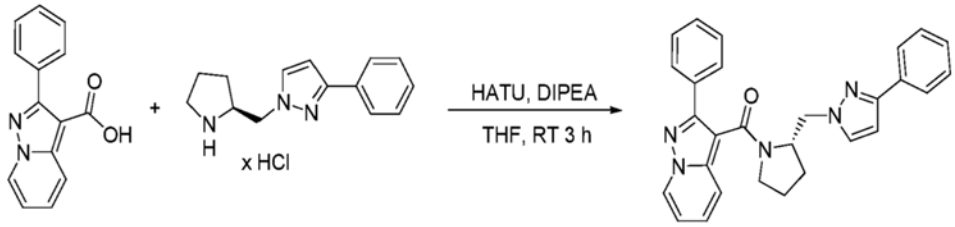
J B **Example 10**



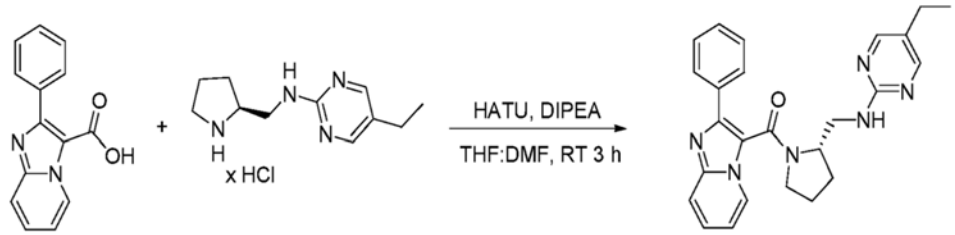
I B **Example 11**



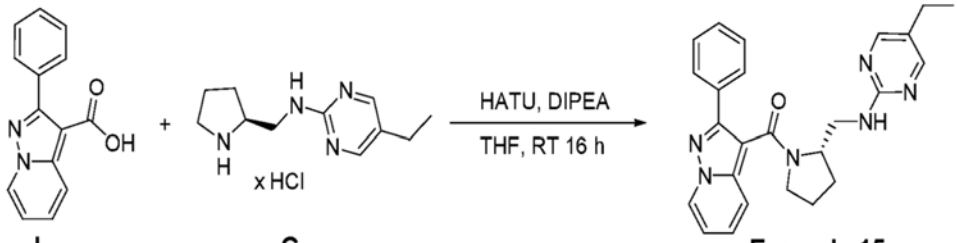
I F **Example 12**



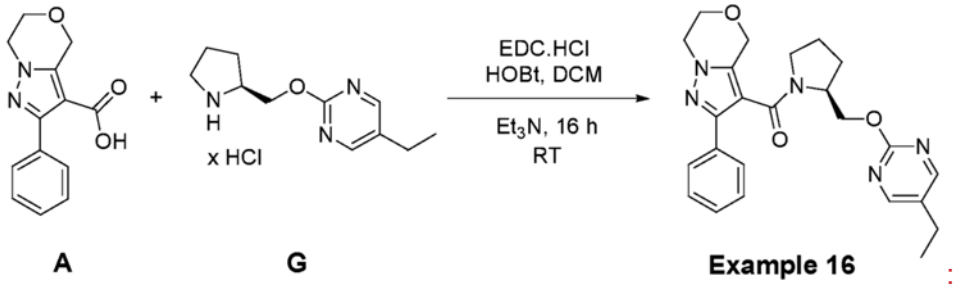
J F **Example 13**



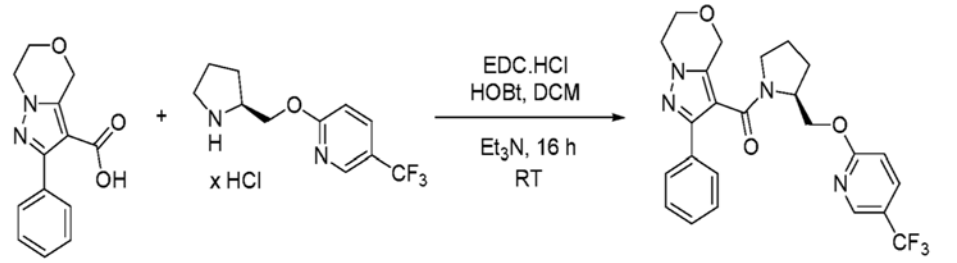
I C **Example 14**



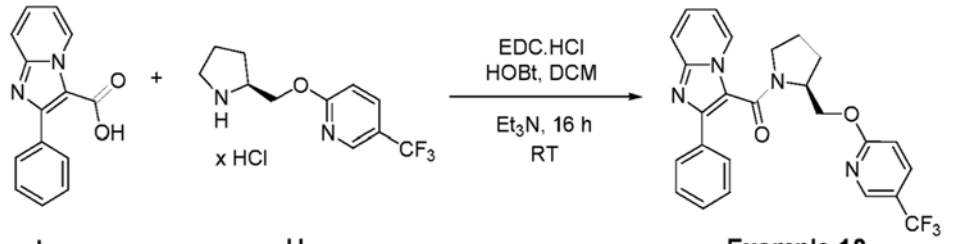
J C **Example 15**



A G Example 16 ;



A H Example 17 ;



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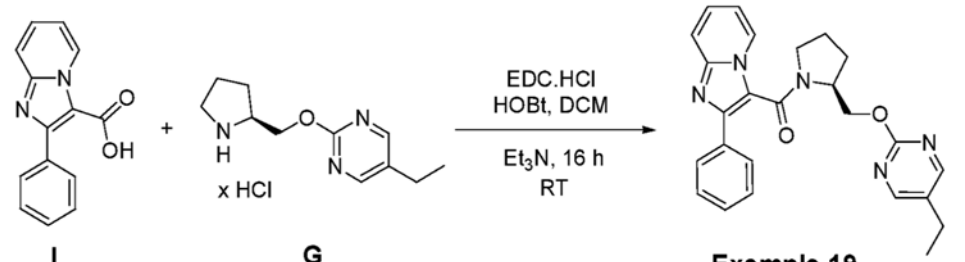
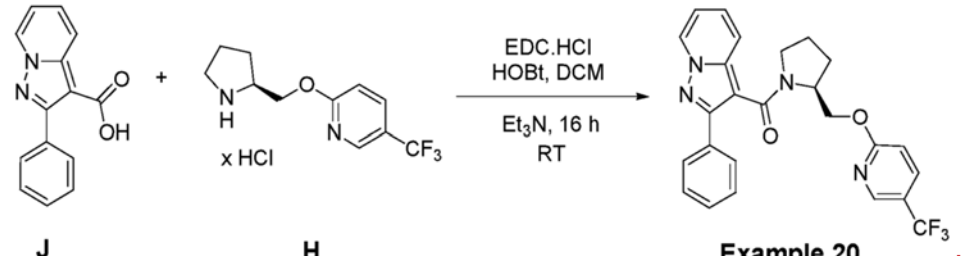
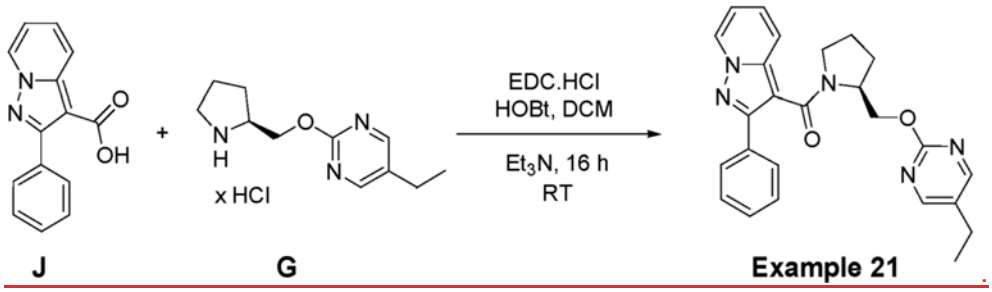


I G Example 19 ;



J H Example 20 ; and,



J G 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.~~

20. The compound according to claim 1, 2, or 3 wherein:

A is N;

B is C or N;

J is C or N;

D is C;

E is C;

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

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

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

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

21. A composition comprising a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, or combination thereof according to claim 20.

22. Use of a compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, or combination thereof, of claim 20 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.