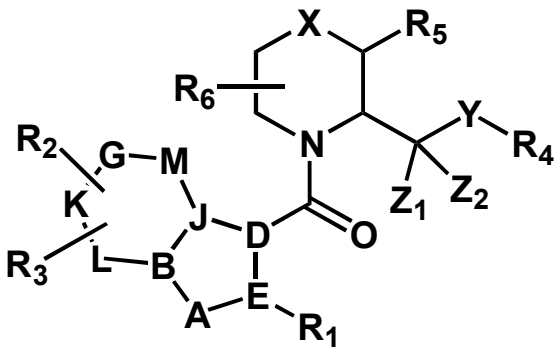
CLAIMS

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 aryl, five or six member heteroaryl, 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 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})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})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 aryl, five or six member heteroaryl; substituted aryl, and substituted five or six member heteroaryl; wherein said 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;

Y is absent or selected from the group consisting of NH, O, CH_2O, 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 aryl, heteroaryl, cycloalkyl, 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,

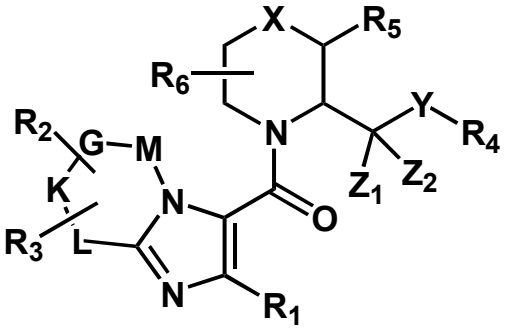
M is selected from the group consisting of C, CH, CR_2R_3, CR_2, CR_3, O; and/or,

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.

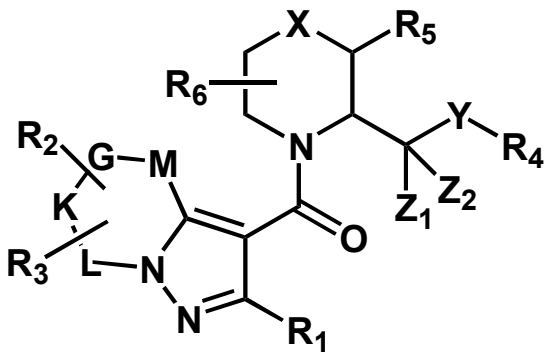
2. A compound according to claim 1, wherein the compound is of formula **II**:



(II)

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

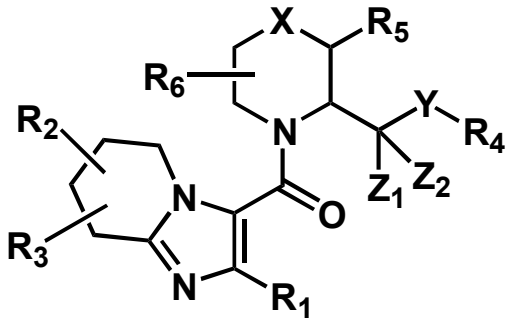
3. A compound according to claim 1, wherein the compound is of formula **III**:



(III)

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

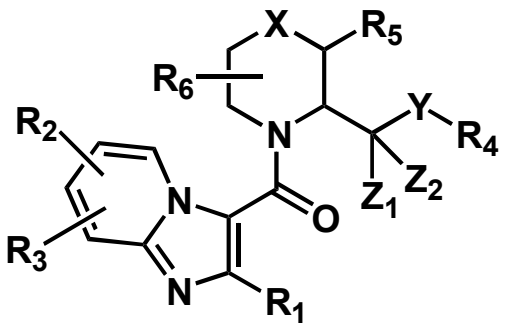
4. A compound according to claim 1, wherein the compound is of formula **II-a**:



(II-a)

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

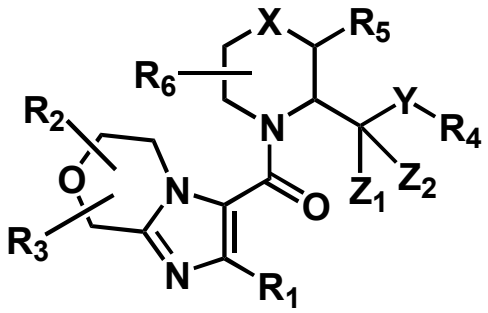
5. A compound according to claim 1, wherein the compound is of formula **II-b**:



(II-b)

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

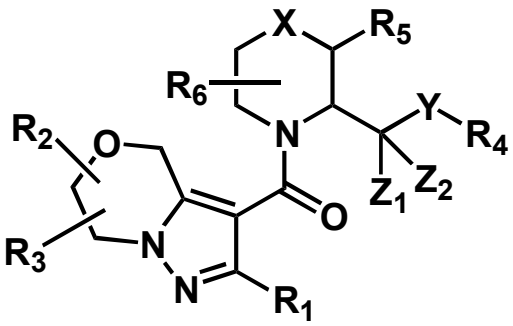
6. A compound according to claim 1, wherein the compound is of formula **II-c**:



(II-c)

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

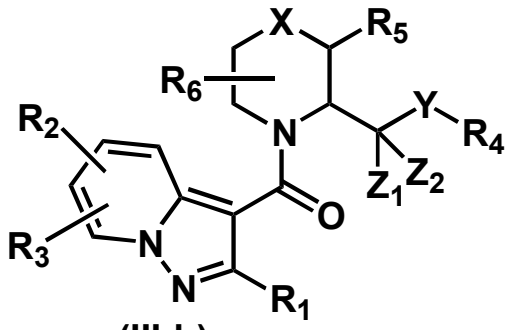
7. A compound according to claim 1, wherein the compound is of formula **III-a**:



(III-a)

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

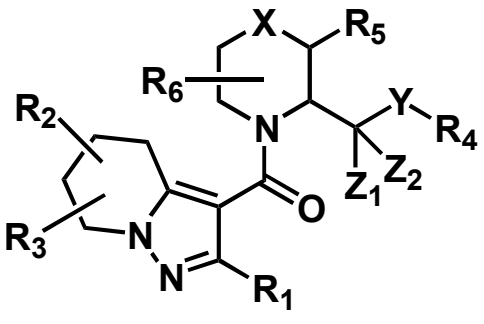
8. A compound according to claim 1, wherein the compound is of formula **III-b**:



(III-b)

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

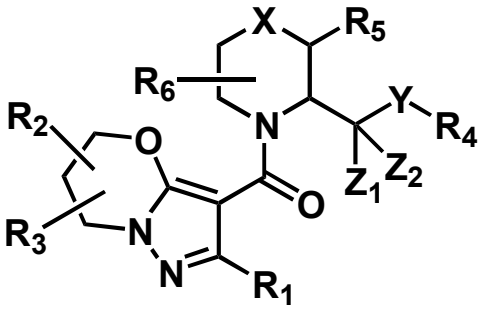
9. A compound according to claim 1, wherein the compound is of formula **III-c**:



(III-c)

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

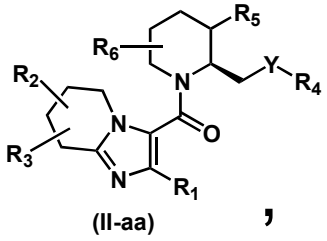
10. A compound according to claim 1, wherein the compound is of formula **III-d**:



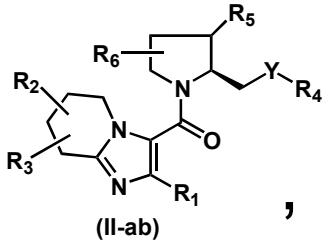
(III-d)

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

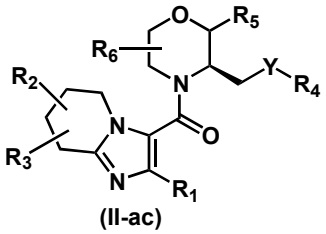
11. A compound according to claim 1, wherein the compound is of formula **II-aa**, **II-ab**, **II-ac, II-ba**, **II-bb**, **II-bc**, **II-ca**, **II-cb**, or **II-cc**:



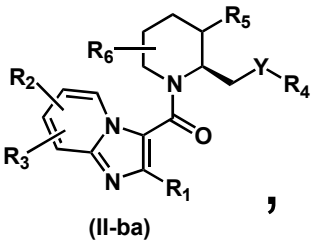
(II-aa) ,



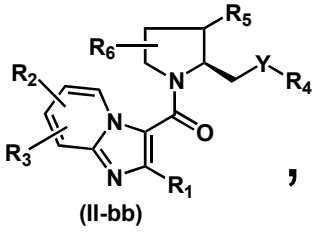
(II-ab) ,



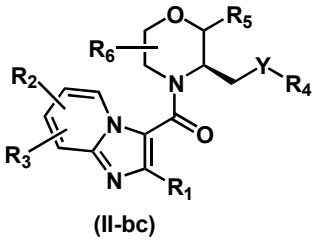
(II-ac)



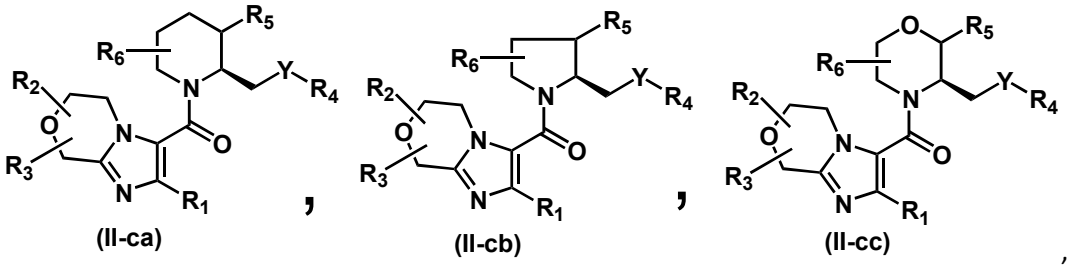
(II-ba) ,



(II-bb) ,

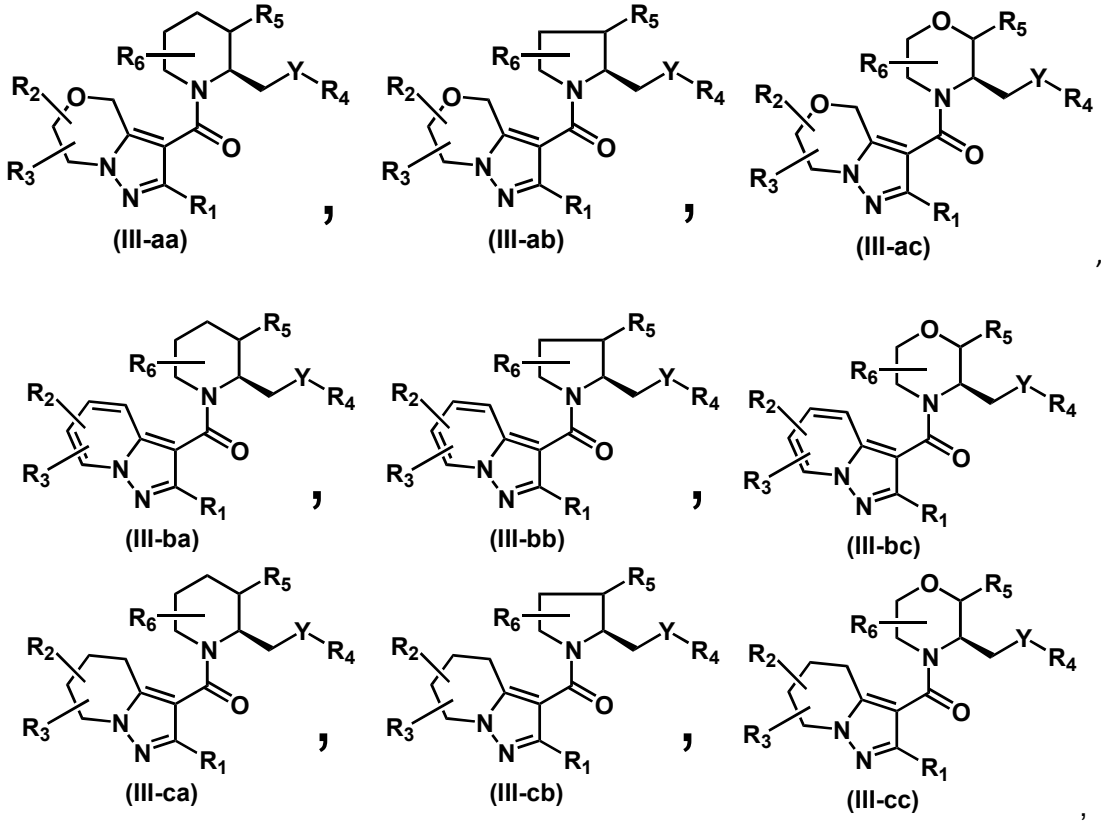


(II-bc)



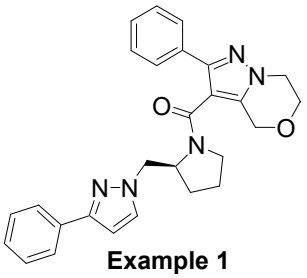
or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer with respect to a stereogenic center, or combination thereof.

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**:



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

13. A compound according to claim 1, wherein the compound is selected from the group consisting of:



Example 1

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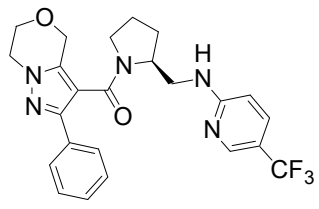

Example 2

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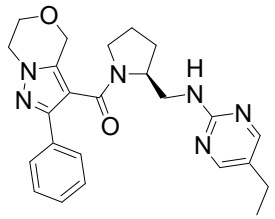

Example 3

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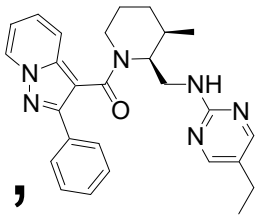
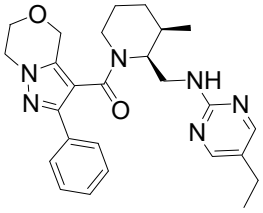


Example 4



Example 5

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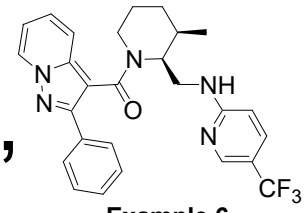

Example 6

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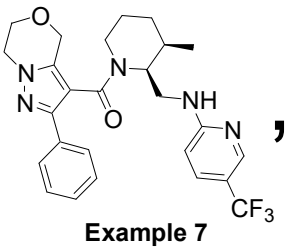

Example 7

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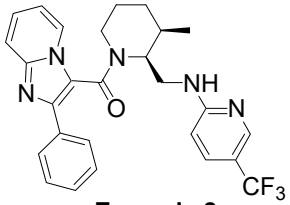
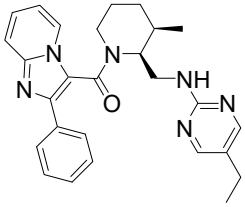


Example 8



Example 9

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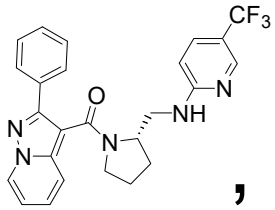

Example 10

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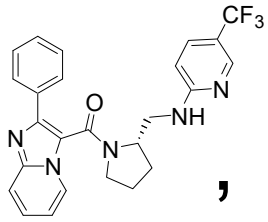

Example 11

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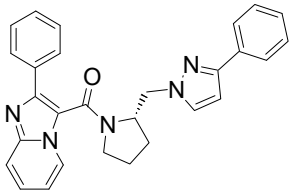
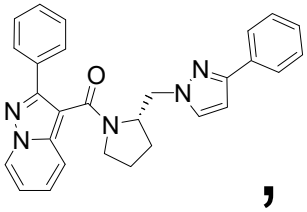


Example 12



Example 13

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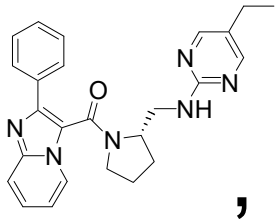

Example 14

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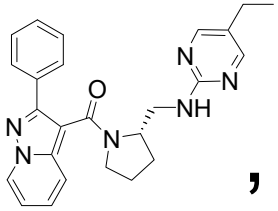

Example 15

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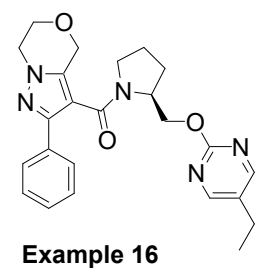
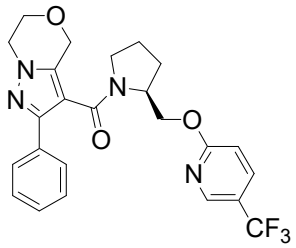


Example 16



Example 17

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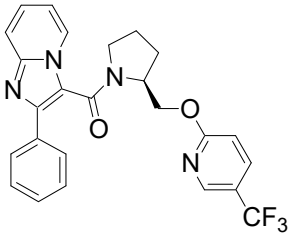

Example 18

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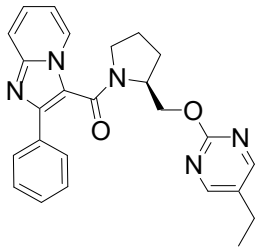

Example 19

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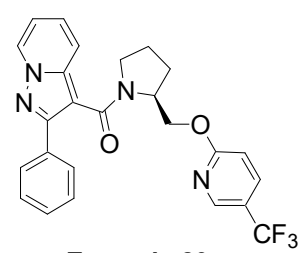
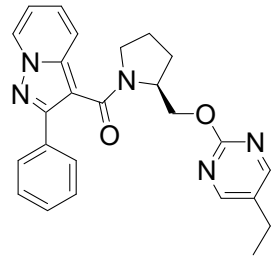


Example 20

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. 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.

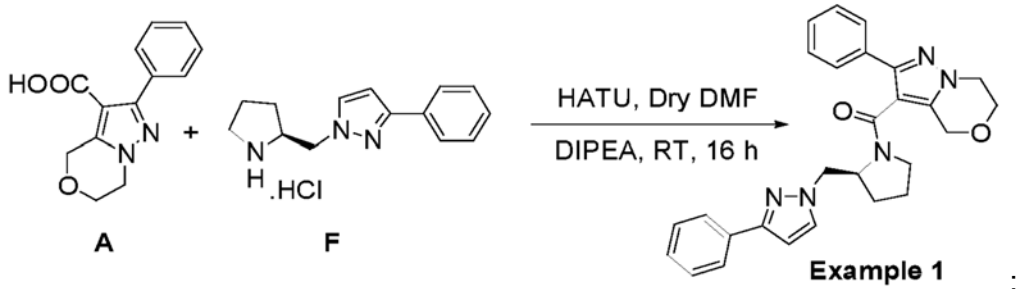
18. The use of claim 17 wherein:

the 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;

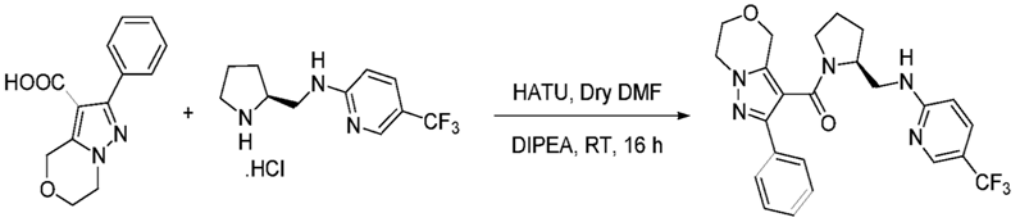
the composition comprises a pharmaceutically acceptable salt or isotope of the compound and/or

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.

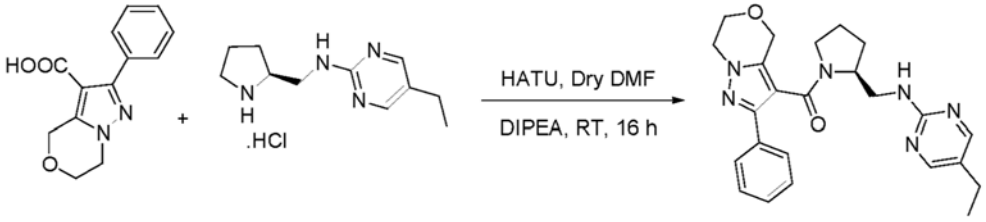
19. A method for preparing a compound, the method comprising a reaction selected from the group consisting of:



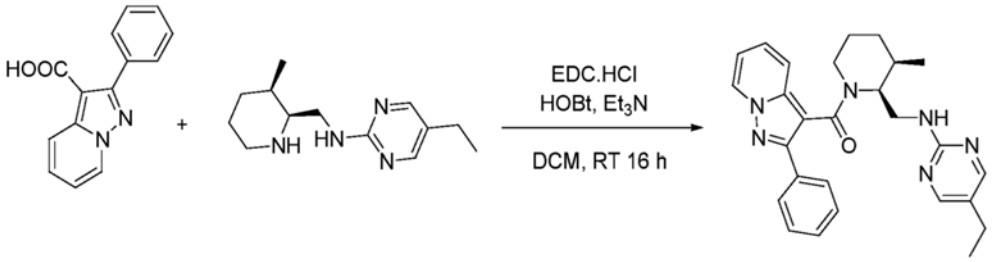
A F Example 1 ;



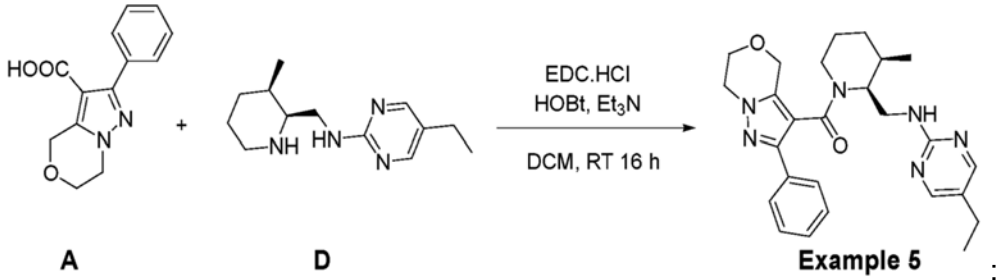
A B Example 2 ;



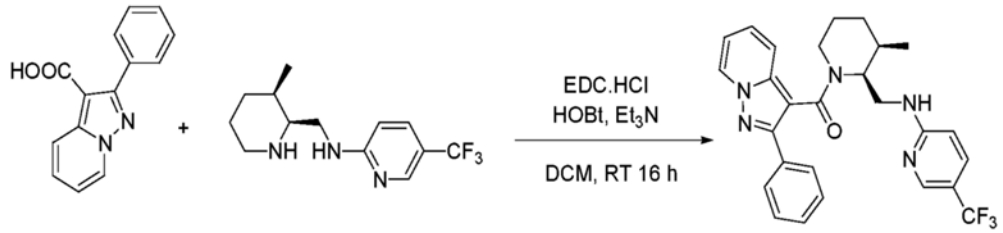
A C Example 3 ;



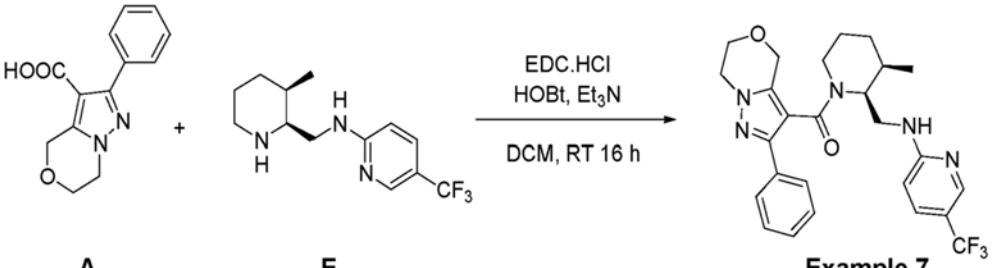
J D **Example 4**



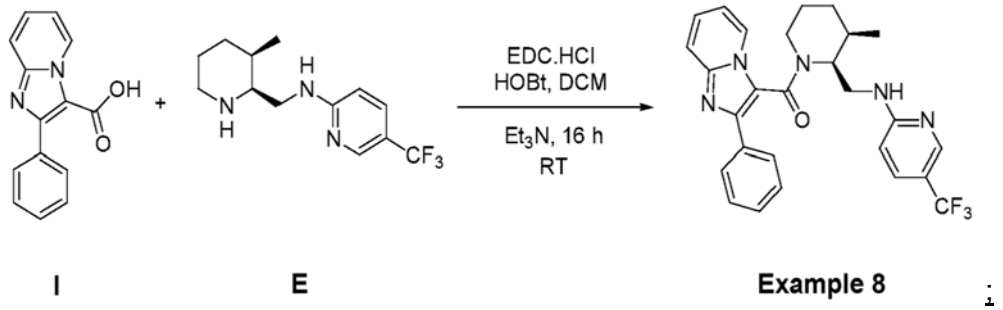
A D **Example 5**



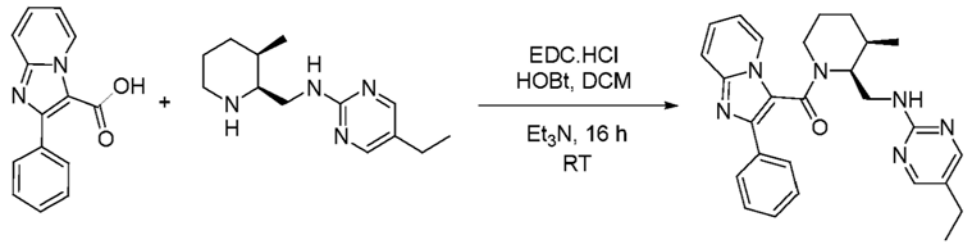
J E **Example 6**



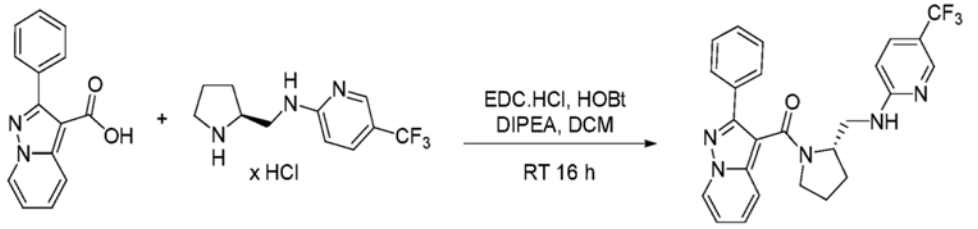
A E **Example 7**



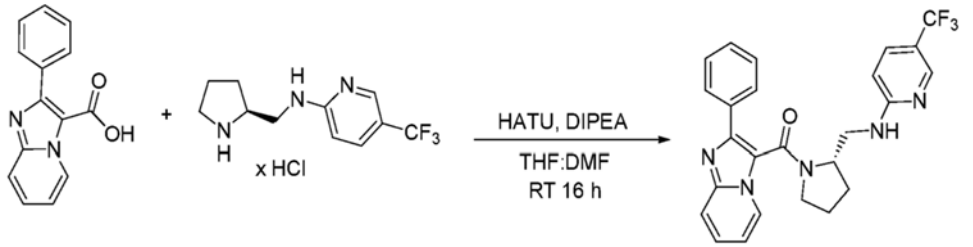
I E **Example 8**



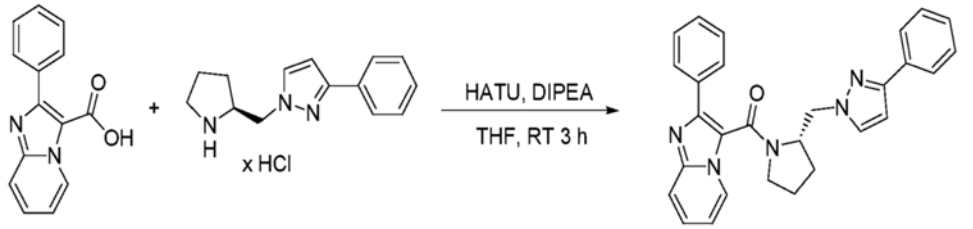
I D **Example 9**



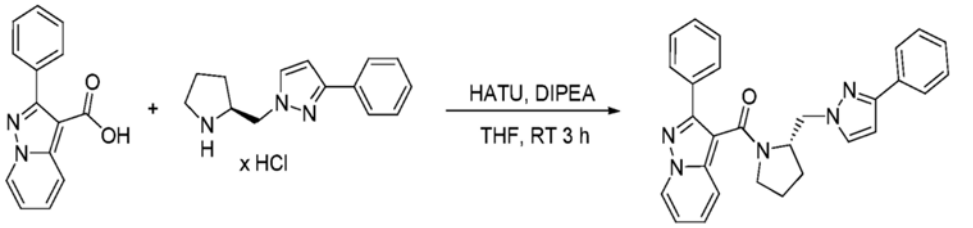
J B **Example 10**



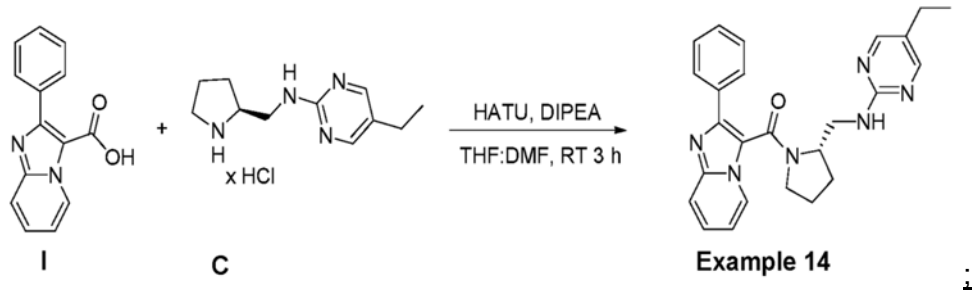
I B **Example 11**



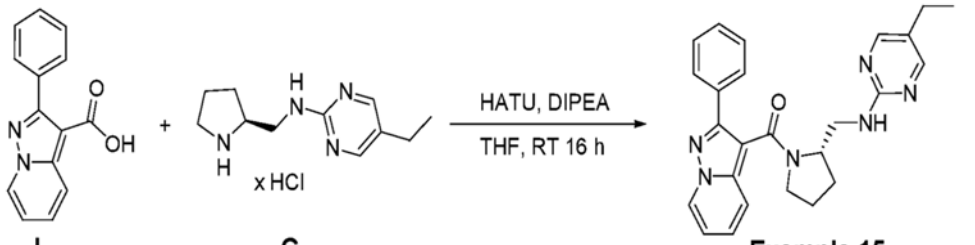
I F **Example 12**



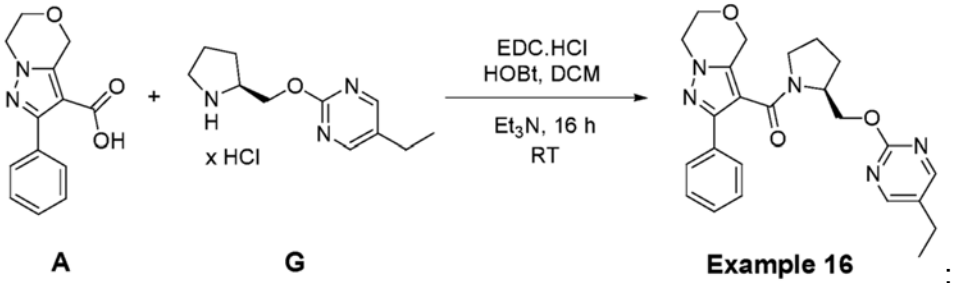
J F **Example 13**



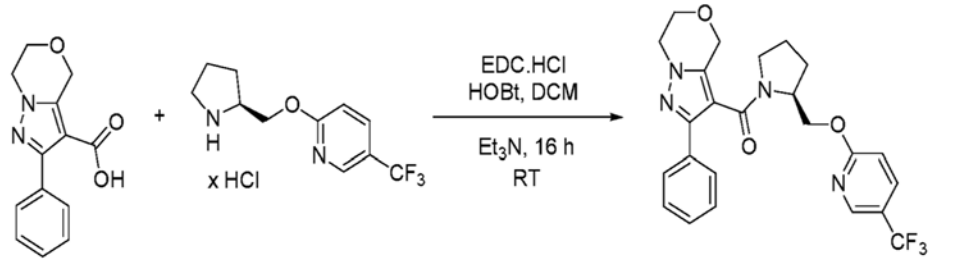
I C **Example 14**



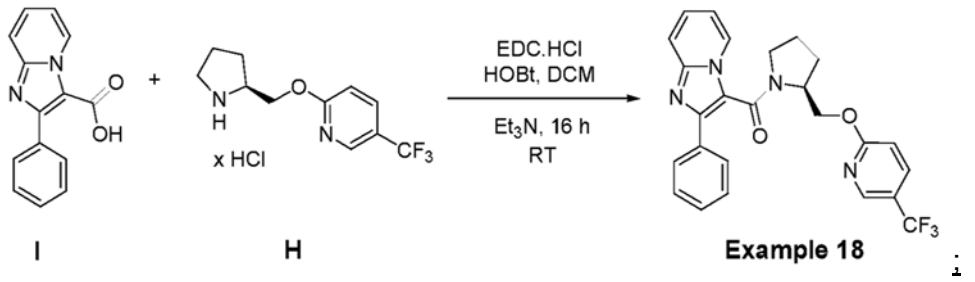
J C **Example 15**



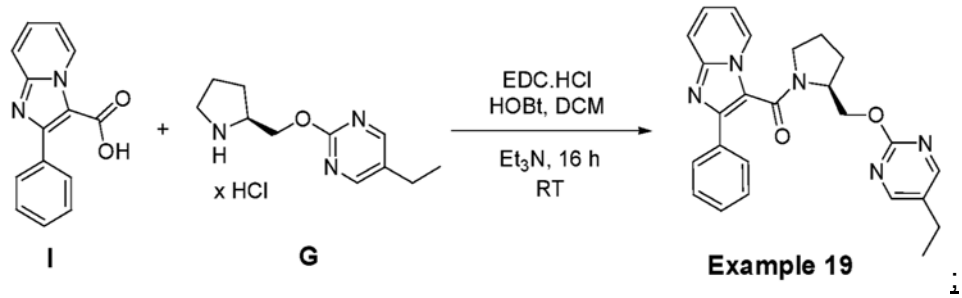
A G **Example 16**



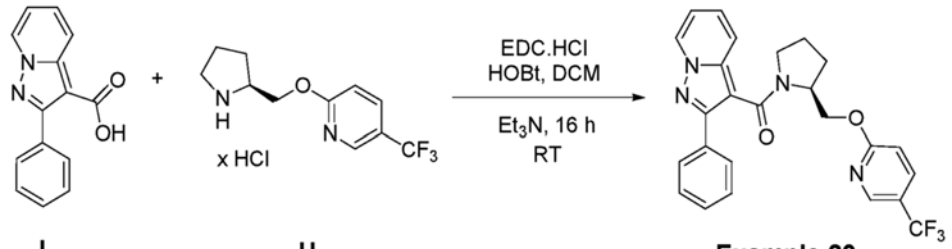
A H **Example 17**



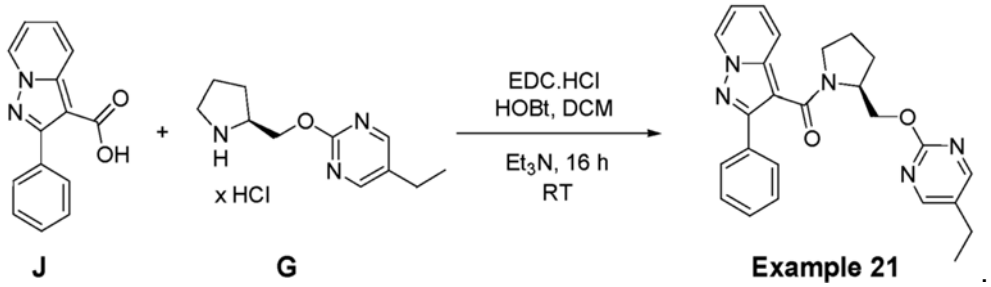
I H **Example 18**



;



; and,



.

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.