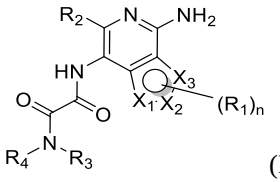
Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof:



(I)

wherein,

X_1, X_2 and X_3 are each independently selected from -CH=, -O-, -S-, -N= or -NH-, and at least one of X_1, X_2 and X_3 is -N= or -NH-, the circle indicating aromaticity;

R_1 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

R_2 is selected from H, C_{1-6} alkyl or halogen;

R_3 and R_4 are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-10 membered heterocyclyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-10 membered heterocyclyl in R_3 or R_4 is each optionally substituted by 1 or 2 R_5, wherein R_5 is selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, SF_5, C_{3-6} cycloalkyl, $-S(O)_2CF_3$, $-OCF_3$, $-SCF_3$, $-SCH_3$ or 5-10 membered heteroaryl; the 5-10 membered heteroaryl is optionally further substituted by R_6, wherein R_6 is selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl, and the 5-6 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

alternatively, R_3, R_4 and the nitrogen atom to which they are attached together form a 4-10 membered heterocyclic group, the 4-10 membered heterocyclic group comprising 0 or 1 additional heteroatom selected from oxygen, nitrogen or sulfur, and being optionally substituted with 1, 2, 3 or 4 R_x;

R_x is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl or 5-10 membered heteroaryl, wherein the phenyl or 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_y;

R_y is selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, CN, OR_a, C_{1-6} alkoxy, $-NR_{z1}R_{z2}$, $NR_{z1}R_{z2}$-C_{1-6} alkyl-, C_{3-6} cycloalkyl, 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 4-12 membered heterocyclyl or 5-10 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

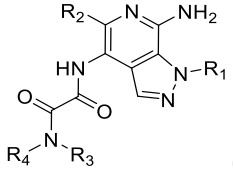
R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy;

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;

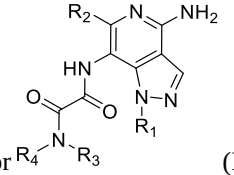
R_{z1} and R_{z2} are each independently selected from H or C_{1-6} alkyl; and

n is 0, 1 or 2.

2. A compound of claim 1, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (IIa) or formula (IIb):



(IIa) or



(IIb)

wherein,

R_1 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

R_2 is selected from H, C_{1-6} alkyl or halogen;

R_3 and R_4 are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-10 membered heterocyclyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-10 membered heterocyclyl in R_3 or R_4 is each optionally substituted by 1 or 2 R_5, wherein R_5 is selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, SF_5, C_{3-6} cycloalkyl, $-S(O)_2CF_3$, $-OCF_3$, $-SCF_3$, $-SCH_3$ or 5-10 membered heteroaryl; the 5-10 membered heteroaryl is optionally further substituted by R_6, wherein R_6 is selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl, the 5-6 membered heteroaryl being optionally substituted by

1, 2 or 3 R_z;

alternatively, R_3, R_4 and the nitrogen atom to which they are attached together form a 4-10 membered heterocyclic group, the 4-10 membered heterocyclic group comprising 0 or 1 additional heteroatom selected from oxygen, nitrogen or sulfur, and being optionally substituted with 1, 2, 3 or 4 R_x;

R_x is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl or 5-10 membered heteroaryl, wherein the phenyl or 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_y;

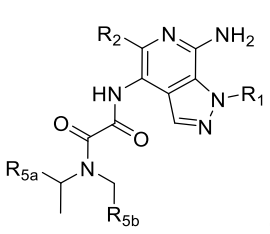
R_y is selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, CN, OR_a, C_{1-6} alkoxy, $-NR_{z1}R_{z2}$, $NR_{z1}R_{z2}$-C_{1-6} alkyl-, C_{3-6} cycloalkyl, 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 4-12 membered heterocyclyl or 5-10 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy;

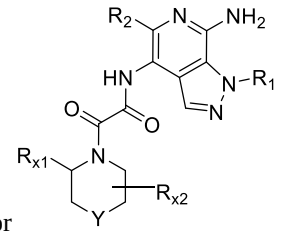
R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; and

R_{z1} and R_{z2} are each independently selected from H or C_{1-6} alkyl.

3. A compound of claim 1 or 2, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, having the following structure:



(III) or



(IV)

wherein:

R_1 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

R_2 is selected from H, methyl, Cl or F;

R_{5a} or R_{5b} are each independently selected from 5-10 membered heteroaryl; the 5-10 membered heteroaryl is optionally substituted by R_6, R_6 being selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl; the 5-6 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_{x1} is selected from phenyl or 5-10 membered heteroaryl, wherein the phenyl or 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_y;

R_y is selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, CN, OR_a, C_{1-6} alkoxy, $-NR_{z1}R_{z2}$, $NR_{z1}R_{z2}$-C_{1-6} alkyl-, C_{3-6} cycloalkyl, 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 4-12 membered heterocyclyl or 5-10 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy;

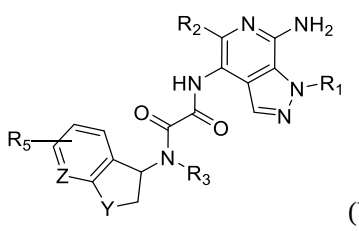
R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;

R_{x2} is selected from C_{1-6} alkyl or C_{1-6} haloalkyl;

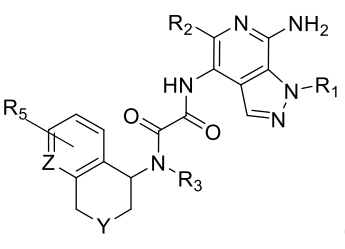
R_{z1} and R_{z2} are each independently selected from H or C_{1-6} alkyl; and

Y is selected from O, S or CH_2.

4. A compound of claim 1 or 2, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, having the following structure:



(VI) or



(VII)

wherein:

R_1 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

R_2 is selected from H, methyl, Cl or F;

R_3 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-10 membered heterocyclyl; the C_{1-6} alkyl or 4-10 membered heterocyclyl is optionally substituted by 1 or 2 R_5;

R_5 is selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, SF_5, C_{3-6} cycloalkyl, $-S(O)_2CF_3$, $-OCF_3$, $-SCF_3$, $-SCH_3$ or 5-10 membered heteroaryl; the 5-10 membered heteroaryl is optionally further substituted with R_6, R_6 being selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl; the 5-6 membered heteroaryl is optionally substituted with 1, 2 or 3 R_z;

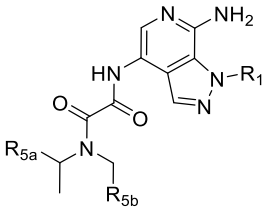
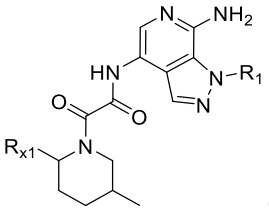
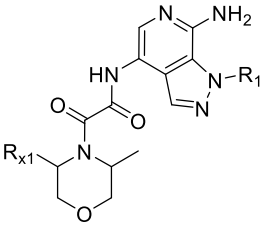
R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy;

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;

Y is selected from NH, O, S or CH_2; and

Z is selected from N or CH.

5. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, having the following structure:


(III-1),

(IV-1) or

(V-1)

wherein,

R_1 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

R_{5a} or R_{5b} are each independently selected from 5-10 membered heteroaryl; the 5-10 membered heteroaryl is optionally substituted by R_6, R_6 being selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl; the 5-6 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_{x1} is selected from phenyl or 5-10 membered heteroaryl, wherein the phenyl or 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_y;

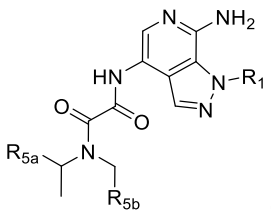
R_y is selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, CN, OR_a, C_{1-6} alkoxy, $-NR_{z1}R_{z2}$, $NR_{z1}R_{z2}$-C_{1-6} alkyl-, C_{3-6} cycloalkyl, 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 4-12 membered heterocyclyl or 5-10 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy;

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; and

R_{z1} and R_{z2} are each independently selected from H or C_{1-6} alkyl.

6. A compound of claim 5, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (III-1):


(III-1)

wherein,

R_1 is selected from methyl, CD_3, ethyl, or cyclopropyl;

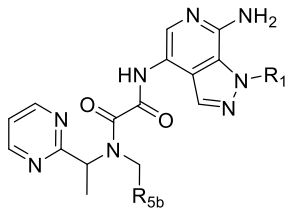
R_{5a} or R_{5b} are each independently selected from 6-membered heteroaryl; the 6-membered heteroaryl is

optionally further substituted by R_6, R_6 being selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6-membered heteroaryl; the 5-6-membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy; and

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

7. A compound of claim 6, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (III-2):



(III-2)

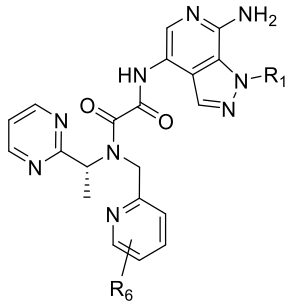
R_1 is selected from methyl, ethyl, or cyclopropyl;

R_{5b} is , which is optionally further substituted by R_6, R_6 being selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl; the 5-6 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy; and

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

8. A compound of claim 7, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (III-3):



(III-3)

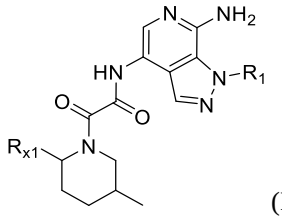
R_1 is selected from methyl, CD_3, ethyl or cyclopropyl;

R_6 is selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl; the 5-6 membered heteroaryl is optionally substituted by 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy; and

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

9. A compound of claim 5, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (IV-1):



(IV-1),

wherein,

R_1 is selected from C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

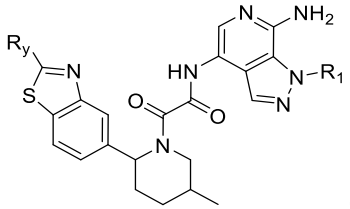
R_{x1} is selected from phenyl or 5-10 membered heteroaryl, wherein the phenyl or 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_y;

R_y is selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, CN, OR_a, C_{1-6} alkoxy, C_{3-6} cycloalkyl, , , 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 4-12 membered heterocyclyl or 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy; and

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

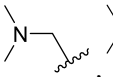
10. A compound of claim 9, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (IV-2):



(IV-2),

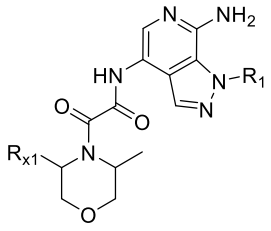
wherein,

R_1 is selected from methyl, CD_3, ethyl or cyclopropyl;

R_y is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, CN, OR_a, C_{1-6} alkoxy, C_{3-6} cycloalkyl, , , 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 4-12 membered heterocyclyl or 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_z; and

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy.

11. A compound of claim 5, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (V-1):



(V-1)

wherein,

R_1 is selected from C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

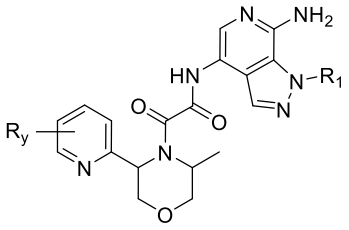
R_{x1} is a 5-10 membered heteroaryl group, which is optionally substituted by 1, 2 or 3 R_y;

R_y is selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, CN, OR_a, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy; and

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

12. A compound of claim 11, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (V-2):



(V-2)

wherein,

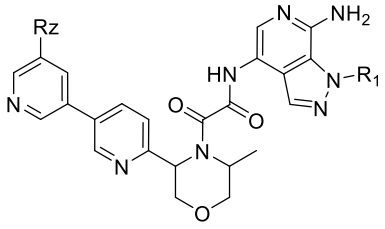
R_1 is selected from methyl, CD_3, ethyl or cyclopropyl;

R_y is selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, CN, OR_a, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 4-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with 1, 2 or 3 R_z;

R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy; and

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

13. A compound of claim 12, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, which is a compound of formula (V-3):



(V-3)

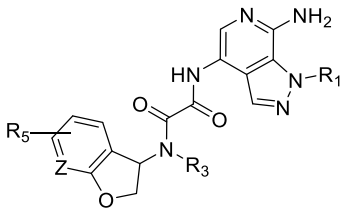
wherein,

R_1 is selected from methyl, CD_3, ethyl or cyclopropyl;

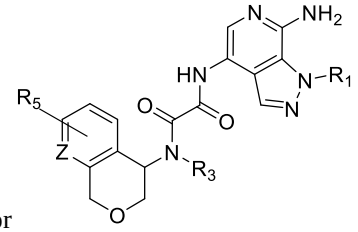
R_z is selected from C_{1-6} alkyl, halogen, CN, C_{1-6} haloalkyl or C_{1-6} alkoxy; and

R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl.

14. A compound of claim 4, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, having the following structure:



(VI-1) or



(VII-1)

wherein:

R_1 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl;

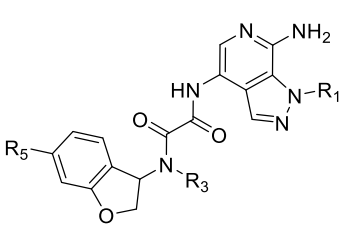
R_3 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-10 membered heterocyclyl; the C_{1-6} alkyl or 4-10 membered heterocyclyl is optionally substituted by 1 or 2 R_5;

R_5 is selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, SF_5, C_{3-6} cycloalkyl, $-S(O)_2CF_3$, $-OCF_3$, $-SCF_3$, $-SCH_3$ or 5-10 membered heteroaryl; the 5-10 membered heteroaryl is optionally further substituted with R_6, R_6 being selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, SF_5, OR_a or 5-6 membered heteroaryl;

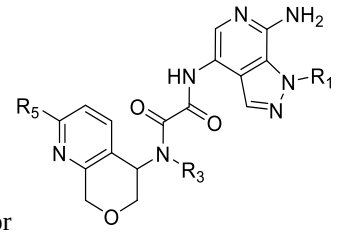
R_a is selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl; and

Z is selected from N or CH.

15. A compound of claim 14, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, having the following structure:



(VI-2) or



(VII-2)

wherein:

R_1 is selected from H, methyl, deuterated methyl, ethyl or cyclopropyl;

R_3 is selected from H, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{3-6} cycloalkyl or 4-10 membered heterocyclyl; and

R_5 is selected from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, SF_5, C_{3-6} cycloalkyl, $-S(O)_2CF_3$, $-OCF_3$, $-SCF_3$, $-SCH_3$ or 5-10 membered heteroaryl.

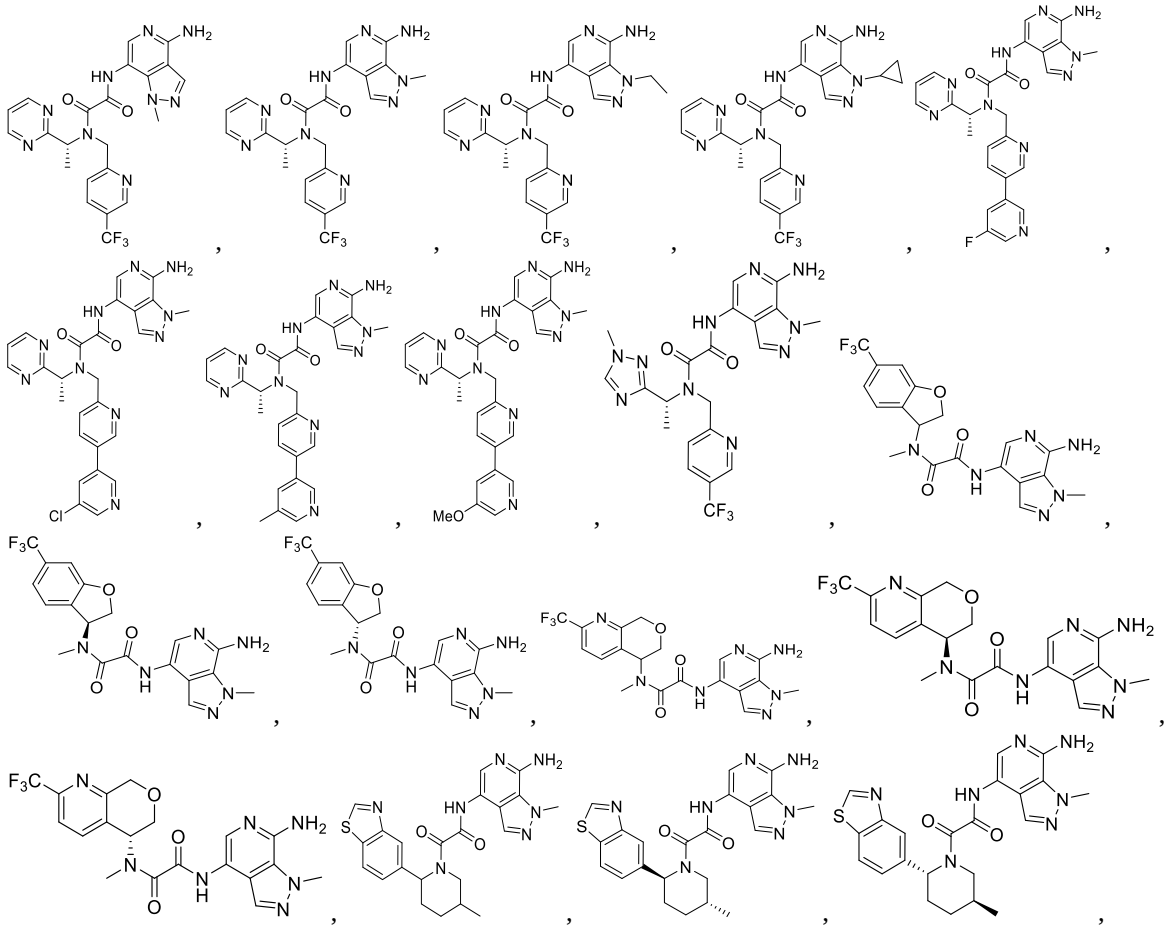
16. A compound of claim 15, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein:

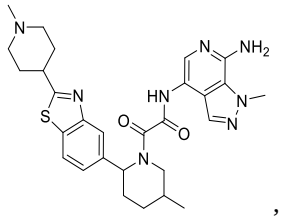
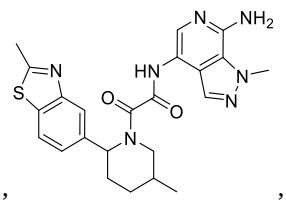
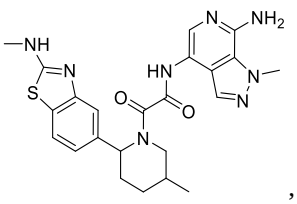
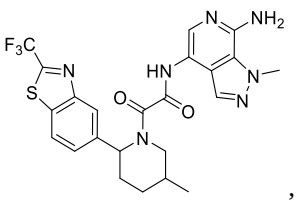
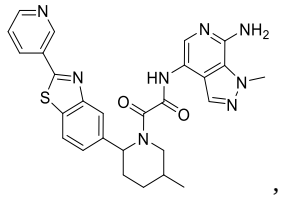
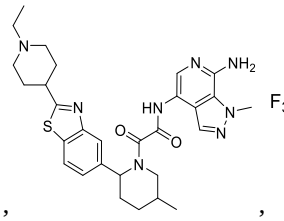
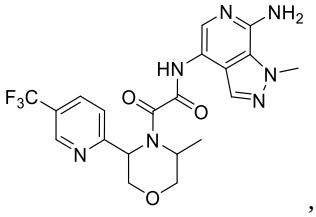
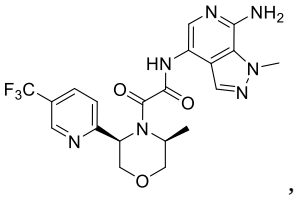
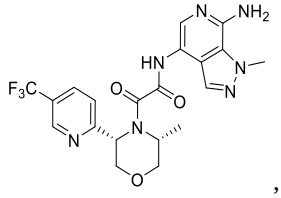
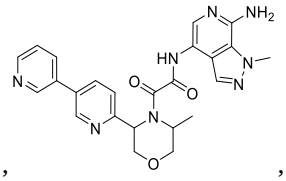
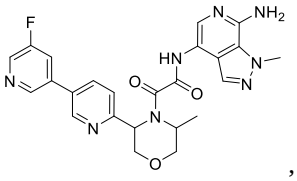
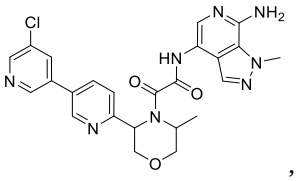
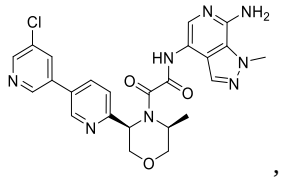
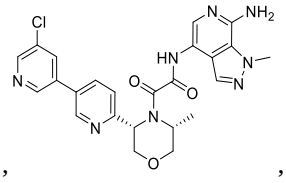
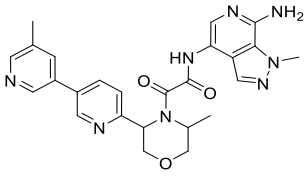
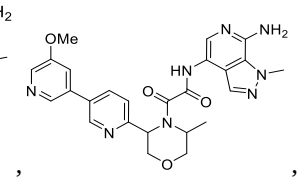
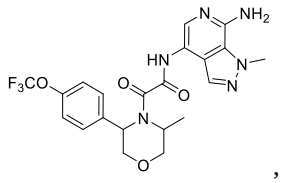
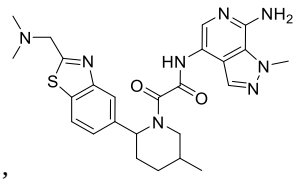
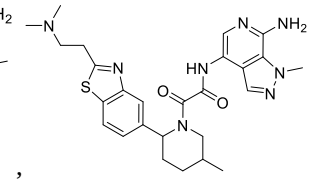
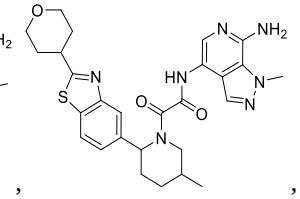
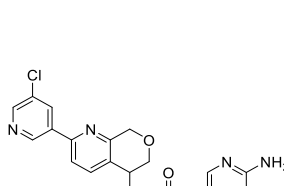
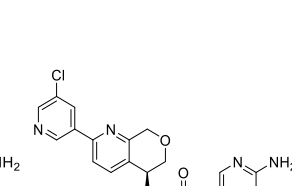
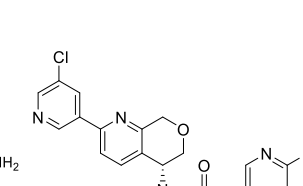
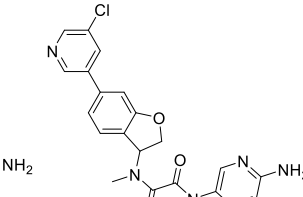
R_1 is selected from H, methyl, CD_3, ethyl or cyclopropyl;

R_3 is selected from H, methyl, CD_3, ethyl or cyclopropyl; and

R_5 is selected from hydrogen, F, Cl, Br, methyl, ethyl, methoxy, trifluoromethyl, difluoromethyl, CN, SF_5, cyclopropyl, $-S(O)_2CF_3$, $-OCF_3$, $-OCF_2Cl$, $-SCF_3$, $-SCH_3$ or pyridyl.

17. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is selected from:

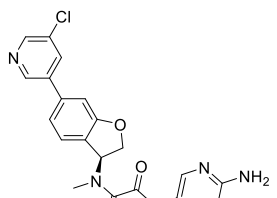
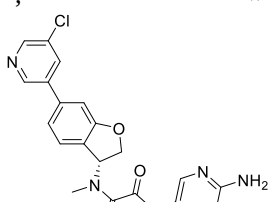
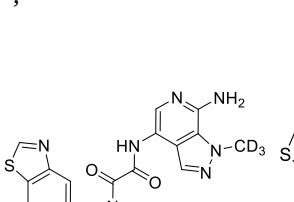
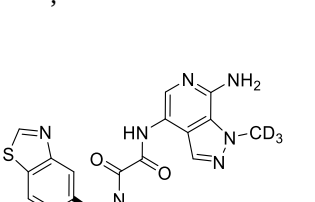
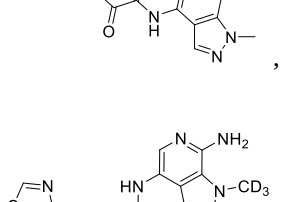
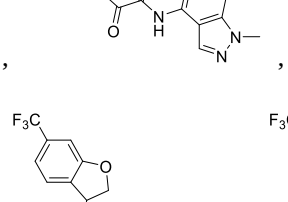
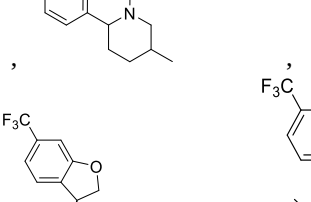
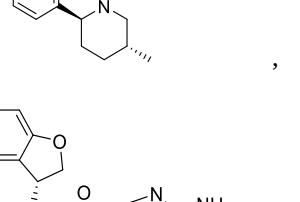
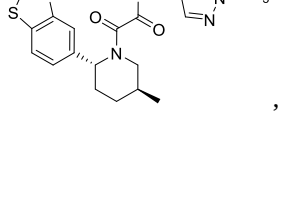
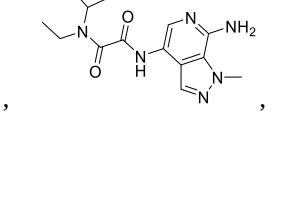
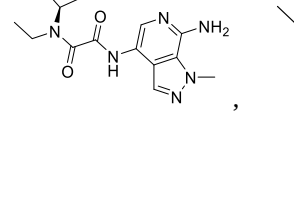
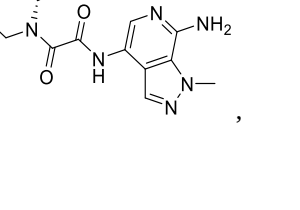


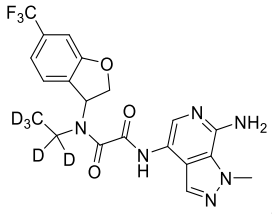
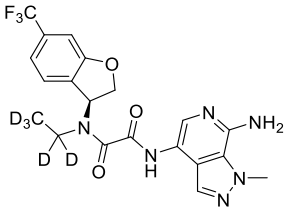
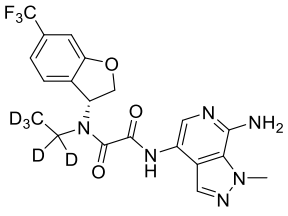
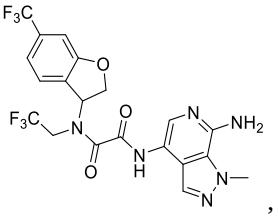
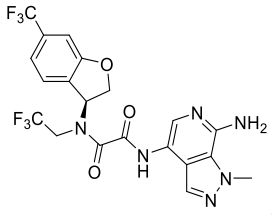
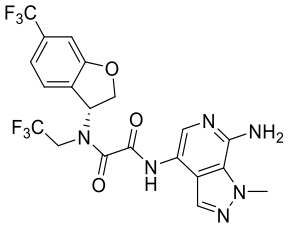
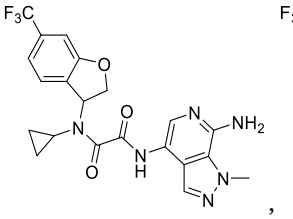
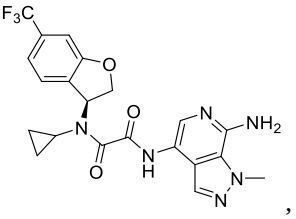
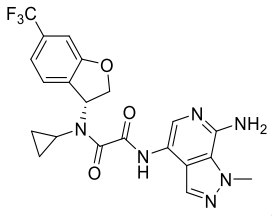
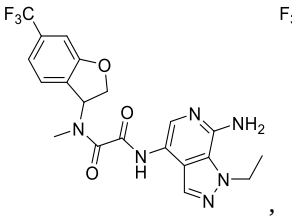
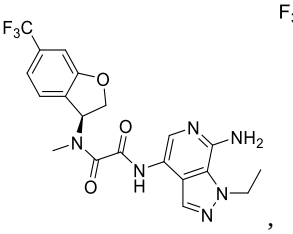
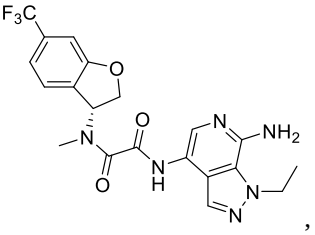
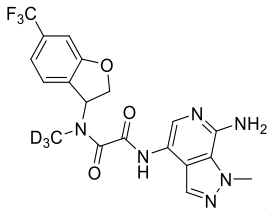
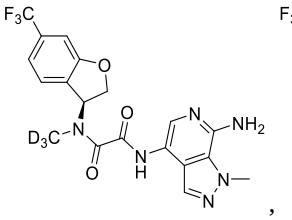
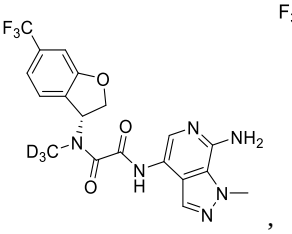
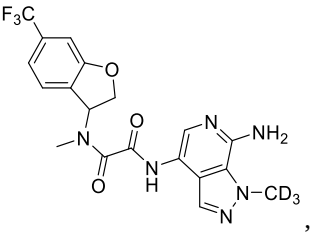
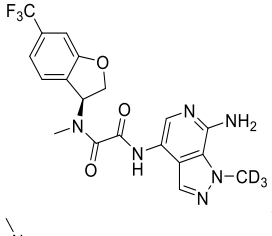
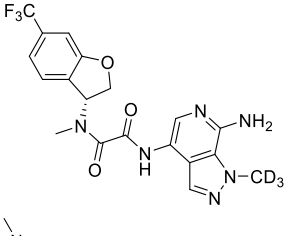
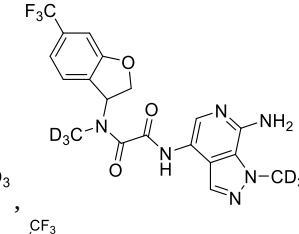
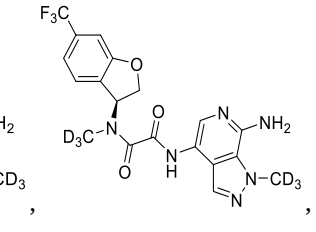
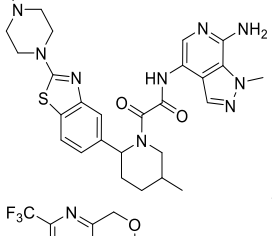
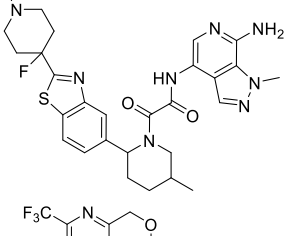
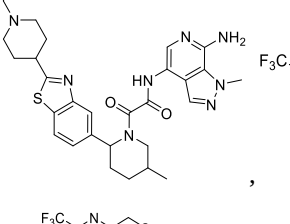
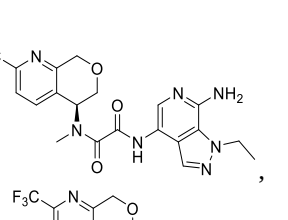
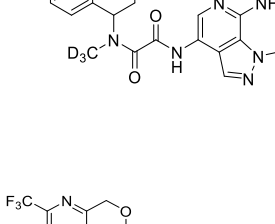
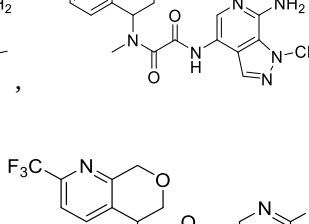
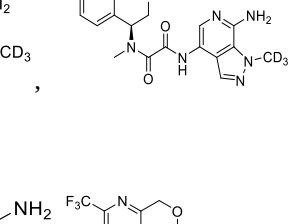
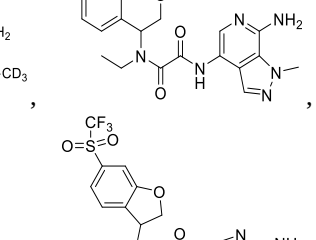
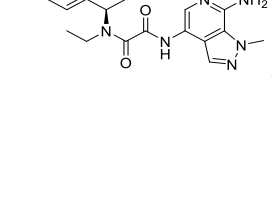
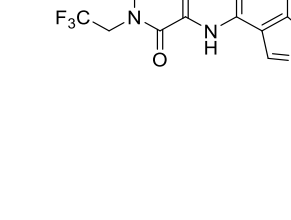
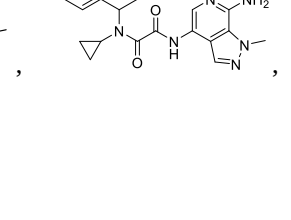
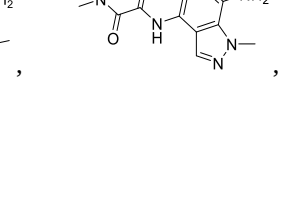

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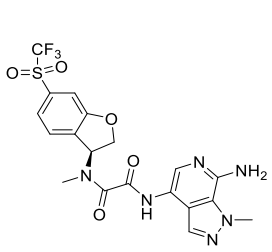
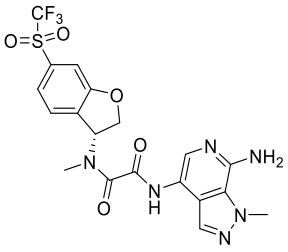
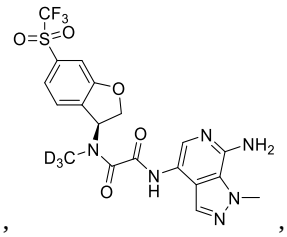

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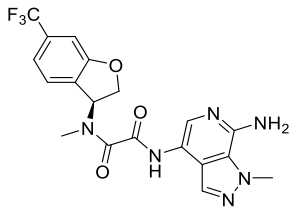
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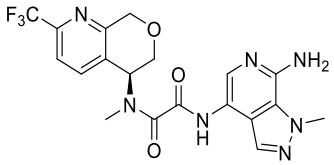
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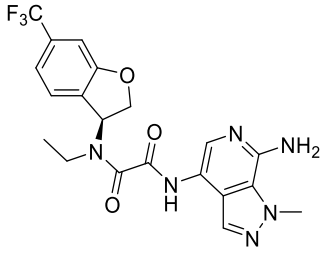
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19. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



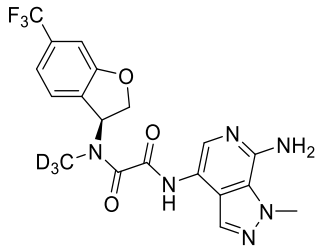
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20. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



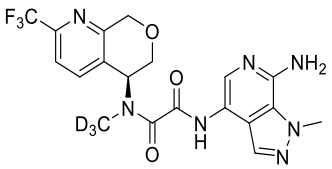
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21. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



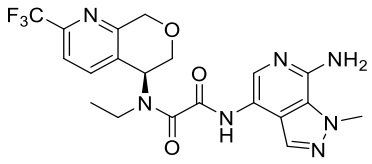
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22. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



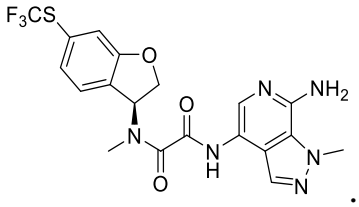
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23. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



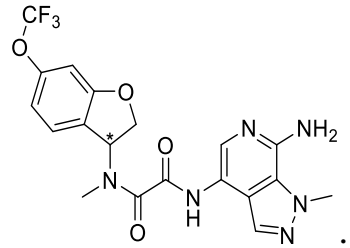
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24. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



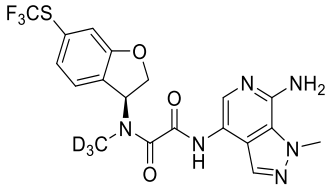
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25. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



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26. A compound, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, wherein the compound is



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27. A pharmaceutical composition comprising a compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof, and a pharmaceutically acceptable excipient; preferably, it further comprises other therapeutic agents.

28. Use of a compound of any one of claims 1 to 26 or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof in the preparation of a medicament for treating and/or preventing a PRMT5 methyltransferase-mediated disease.

29. A compound of any one of claims 1 to 26 or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof or a pharmaceutical composition of claim 27 for use in treating and/or preventing a PRMT5 methyltransferase-mediated disease.

30. The use of claim 28 or the compound or composition of claim 29, wherein the PRMT5 methyltransferase-mediated disease is cancer, and the cancer is selected from the group consisting of: acoustic neuroma, adenocarcinoma, adrenal cancer, anal cancer, angiosarcoma (e.g., lymphangiosarcoma, lymphangioendothelial sarcoma, hemangioma), appendix cancer, benign monoclonal gammopathy, bile duct cancer, bladder cancer, brain cancer (e.g., meningioma, glioma, such as astrocytoma, oligodendroglioma, medulloblastoma), bronchogenic carcinoma, carcinoid tumor, cervical cancer (e.g. cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (e.g. colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial

cancer, ependymoma, endothelial sarcoma (e.g. Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (e.g. uterine cancer, uterine sarcoma), esophageal cancer (e.g. esophageal adenocarcinoma, Barrett's adenocarcinoma), Ewing's sarcoma, eye cancer (e.g. intraocular melanoma, retinoblastoma), hypereosinophilia, gallbladder cancer, gastric cancer (e.g., gastric adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma), oral cancer (e.g., oral squamous cell carcinoma), laryngeal cancer (e.g., laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)), hematopoietic system cancer (e.g., leukemias, such as acute lymphoblastic leukemia (ALL) (e.g., B-cell ALL, T-cell ALL), acute myeloid leukemia (AML) (e.g., B-cell AML, T-cell AML), chronic myeloid leukemia (CML) (e.g., B-cell CML, T-cell CML), chronic lymphocytic leukemia (CLL) (e.g., B-cell CLL, T-cell CLL), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma (e.g., mucosa-associated lymphoid tissue (MALT) lymphoma, lymph node marginal zone B-cell lymphoma, splenic marginal zone mediastinal B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt's lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and primary central nervous system (CNS) lymphoma; and T-cell non-Hodgkin lymphoma, such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (e.g., cutaneous T-cell lymphoma (e.g., mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy-associated T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma); a mixture of one or more of the above leukemias/lymphomas; multiple myeloma (MM), heavy chain disease (e.g., α-chain disease, γ-chain disease, μ-chain disease), hemangioblastoma, inflammatory myofibroblastic tumor, immunocytic amyloidosis, renal cancer (e.g., Wilms tumor, renal cell carcinoma), liver cancer (e.g., hepatocellular carcinoma, malignant hepatocellular carcinoma), lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), lung adenocarcinoma, leiomyosarcoma (LMS), mastocytosis (e.g., systemic mastocytosis), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorders (MPDs) (e.g., polycythemia vera (PV), essential thrombocythemia (ET), agnogenic myeloid metaplasia (AMM), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES), neuroblastoma, neurofibromas (e.g., neurofibromatosis type 1 or type 2, schwannomatosis), neuroendocrine cancer (e.g., gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, or penile cancer.