

We claim

1. A compound of formula (IIa), a stereoisomer or pharmaceutically acceptable salt thereof:



(IIa)

wherein, X_1 is -O- or -CH₂-;

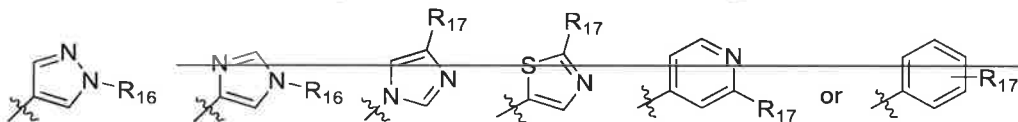
X_2 is bond, -O- or -CH₂-;

Z_5 is CH or N;

R_1 and R_2 are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, methyl, ethyl, propyl, cyclopropyl, cyclopropylmethyl, methoxy, ethoxy, phenylmethoxy, methoxyethyl, hydroxymethyl, cyanomethyl, trifluoromethyl, trideuteriomethyl, difluoromethyl, dideuteriomethyl and aminomethyl, or, R_1 and R_2 , together with the carbon atom directly attached thereto, form C₃₋₆ cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, methyl, ethyl, cyclopropyl, cyclopropylmethyl, trifluoromethyl, trideuteriomethyl, difluoromethyl and dideuteriomethyl;

R_4 is selected from C₅₋₈ aryl, 5-8 membered heteroaryl or -NR₁₄R₁₅, wherein said C₅₋₈ aryl and 5-8 membered heteroaryl are selected from the following structures:



wherein, each R_{16} is independently selected from the group consisting of hydrogen, deuterium, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₁, -C₀₋₄-C(O)OR₁₂ and -C₀₋₄-C(O)R₁₃, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₁, -C₀₋₄-O-R₁₂, -C₀₋₄-C(O)OR₁₂, -C₀₋₄-C(O)R₁₃, -C₀₋₄-O-C(O)R₁₃, -C₀₋₄-NR₁₄R₁₅, -C₀₋₄-C(O)NR₁₄R₁₅ and -C₀₋₄-N(R₁₄)-C(O)R₁₃, wherein the cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₁, -C₀₋₄-O-R₁₂, -C₀₋₄-C(O)OR₁₂, -C₀₋₄-C(O)R₁₃, -C₀₋₄-O-C(O)R₁₃, -C₀₋₄-NR₁₄R₁₅, -C₀₋₄-C(O)NR₁₄R₁₅ and -C₀₋₄-N(R₁₄)-C(O)R₁₃;

each R_{17} is independently selected from the group consisting of hydrogen, deuterium, halogen, cyano, nitro, azido, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₁,

~~C₀₋₄-O-R₁₂~~—~~C₀₋₄-C(O)OR₁₂~~—~~C₀₋₄-C(O)R₁₃~~—~~C₀₋₄-O-C(O)R₁₃~~—~~C₀₋₄-NR₁₄R₁₅~~
~~C₀₋₄-C(O)NR₁₄R₁₅~~ and ~~C₀₋₄-N(R₁₄)-C(O)R₁₃~~

above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, C₀₋₄S(O)_rR₁₁, C₀₋₄O R₁₂, C₀₋₄C(O)OR₁₂, C₀₋₄C(O)R₁₃, C₀₋₄O C(O)R₁₃, C₀₋₄NR₁₄R₁₅, C₀₋₄C(O)NR₁₄R₁₅ and C₀₋₄N(R₁₄)C(O)R₁₃, wherein the cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally more further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, C₀₋₄S(O)_rR₁₁, C₀₋₄O R₁₂, C₀₋₄C(O)OR₁₂, C₀₋₄C(O)R₁₃, C₀₋₄O C(O)R₁₃, C₀₋₄NR₁₄R₁₅, C₀₋₄C(O)NR₁₄R₁₅ and C₀₋₄N(R₁₄)C(O)R₁₃;

each R₁₁ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₂₋₈ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₄R₁₅, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, carbonyl, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₄R₁₅;

each R₁₂ is independently selected from the group consisting of hydrogen, deuterium, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl and 5-10 membered heteroaryl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, carbonyl, cyano, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₄R₁₅;

each R₁₃ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₄R₁₅, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, cyano, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₄R₁₅;

each of R₁₄ and R₁₅ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, sulfonyl, methanesulfonyl, isopropylsulfonyl, cyclopropylsulfonyl, p-toluenesulfonyl, amino, monoalkylamino, dialkylamino and C₁₋₈ alkanoyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy, amino, monoalkylamino, dialkylamino and C₁₋₈ alkanoyl;

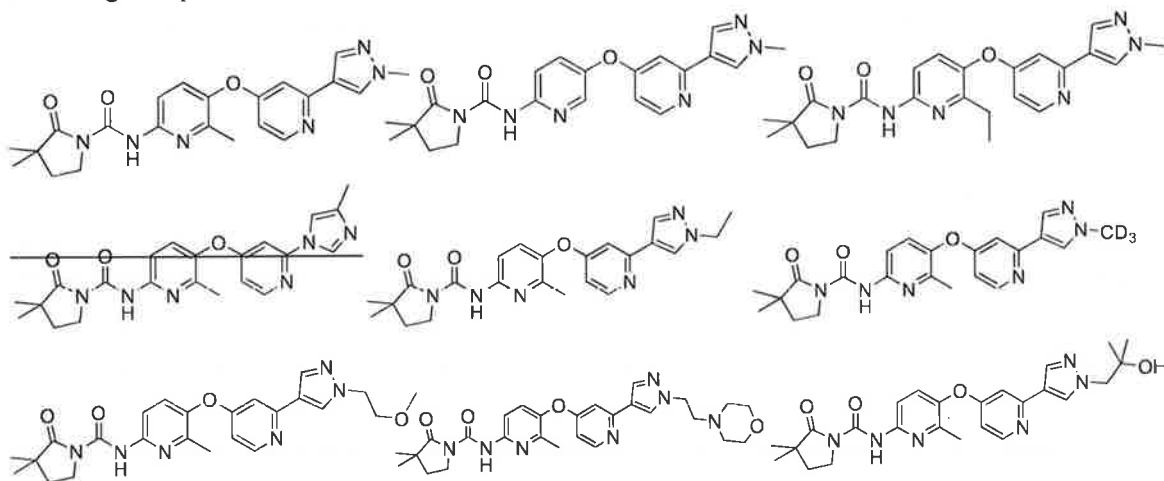
or R₁₄ and R₁₅, together with nitrogen atom directly attached thereto, form 5-10 membered heterocyclyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy, amino, monoalkylamino, dialkylamino and C₁₋₈ alkanoyl; and r is 0, 1 or 2.

2. The compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein each R₁₆ is ~~independently~~ selected from the group consisting of hydrogen, deuterium, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl and 5-6 membered heteroaryl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₁, -C₀₋₄-O-R₁₂, -C₀₋₄-C(O)OR₁₂, -C₀₋₄-C(O)R₁₃, -C₀₋₄-O-C(O)R₁₃, -C₀₋₄-NR₁₄R₁₅, -C₀₋₄-C(O)NR₁₄R₁₅ and -C₀₋₄-N(R₁₄)-C(O)R₁₃;

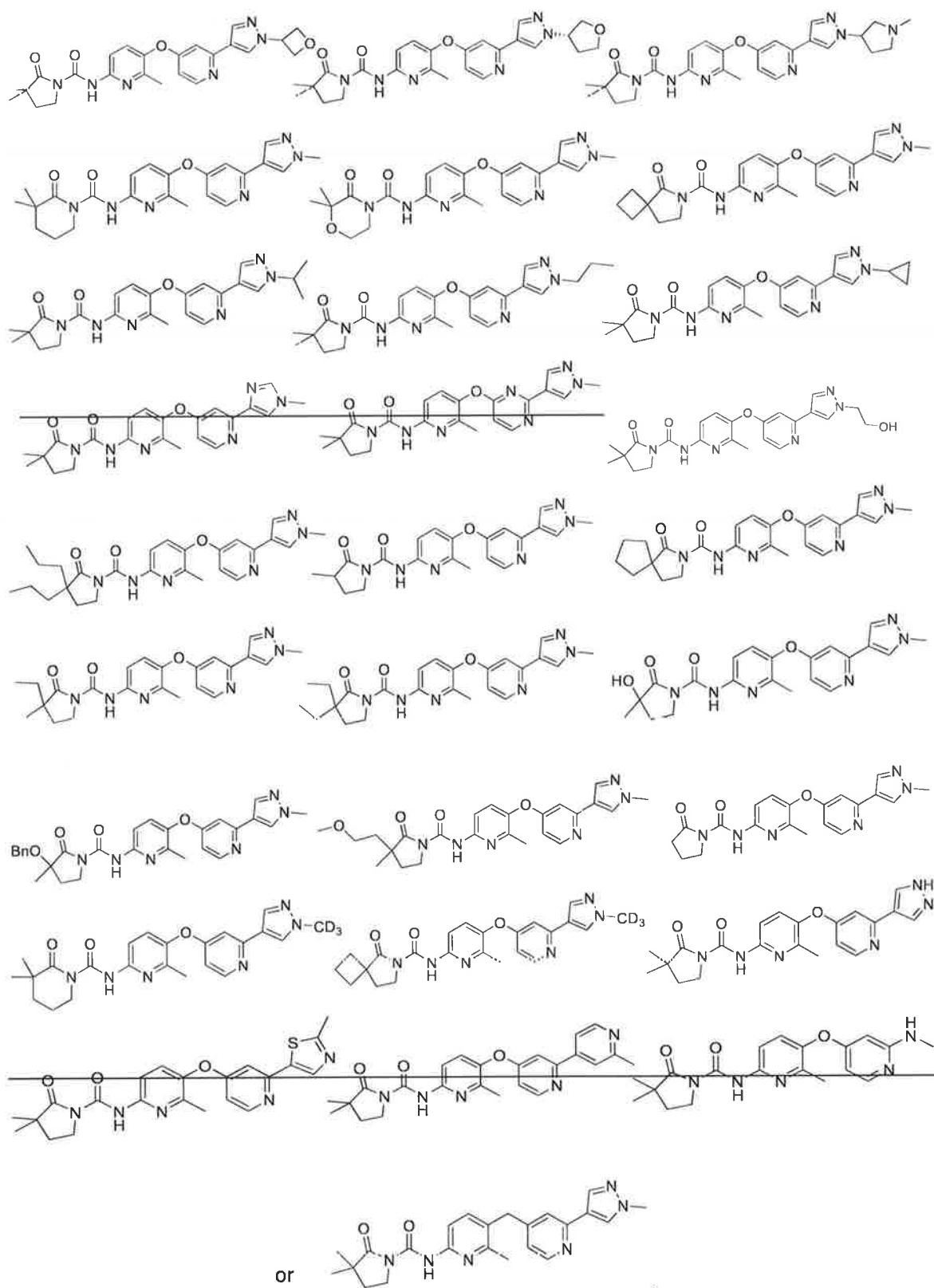
~~each R₁₇ is independently selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, nitro, azido, methyl, ethyl, isopropyl, allyl, ethynyl, cyclopropyl, cyclopropylmethyl, oxa-cyclobutyl, aza-cyclopentyl, aza-cyclohexyl, phenyl, diazole, triazole, methanesulfonyl, isopropylsulfonyl, aminosulfonyl, methoxy, ethoxy, isopropoxy, methoxyethyl, ethoxyethyl, hydroxymethyl, hydroxyethyl, cyanomethyl, trifluoromethyl, trideuteriomethyl, difluoromethyl, dideuteriomethyl, methoxycarbonyl, ethoxycarbonyl, acetyl, acetoxymethyl, amino, dimethylamino, aminomethyl, aminocarbonyl, dimethylaminocarbonyl and acetylamino;~~

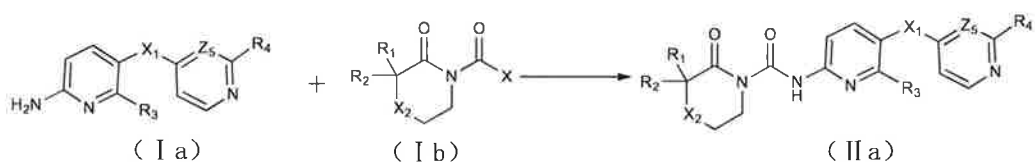
wherein, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, and r are defined as in claim 1.

3. The compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 2, wherein the compound is selected from the following compounds:



reaction of the compound of formula (Ia) or an acidic salt thereof and the compound of formula (Ib), and the reaction equation is as follows:





wherein, X is chlorine ~~or~~ bromine ~~or~~ carboxyl; X₁, X₂, Z₅, R₁, R₂, R₃, and R₄ are defined as in claim 1.

5 5. A pharmaceutical composition, comprising the compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, and a pharmaceutically acceptable carrier.

10 6. Use of the compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, or the pharmaceutical composition of claim 5 in the preparation of medicament for treating cancer, tumor, autoimmune disease, metabolic disease or metastatic disease.

15 7. Use of the compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, or the pharmaceutical composition of claim 5 in the preparation of medicament for treating ovarian cancer, pancreatic cancer, prostate cancer, lung cancer, breast cancer, renal carcinoma, liver cancer, cervical cancer, osseous metastasis cancer, papillary thyroid cancer, non-small cell lung cancer, colon cancer, gastrointestinal stromal tumor, solid tumor, melanoma, mesothelioma, glioblastoma, osteosarcoma, multiple myeloma, hyperproliferative disease, metabolic disease, neurodegenerative disease, primary tumor site metastasis, myeloproliferative disease, leukemia, rheumatic arthritis, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, hypereosinophilic syndrome, mastocytosis or mast cell leukemia.

25 8. Use of the compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, or the pharmaceutical composition of claim 5 in the preparation of medicament for treating ovarian cancer, pancreatic cancer, prostate cancer, breast cancer, cervical cancer, glioblastoma, multiple myeloma, metabolic disease, neurodegenerative disease, primary tumor site metastasis or osseous metastasis cancer.

35 9. The compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, or the pharmaceutical composition of claim 5 for use as a medicament for treating ovarian cancer, pancreatic cancer, prostate cancer, lung cancer, breast cancer, renal carcinoma, liver cancer, cervical cancer, osseous metastasis cancer, papillary thyroid cancer, non-small cell lung cancer, colon cancer, gastrointestinal stromal tumor, solid tumor, melanoma, mesothelioma, glioblastoma, osteosarcoma, multiple myeloma, hyperproliferative disease, metabolic disease, neurodegenerative disease, primary tumor site metastasis, myeloproliferative disease, leukemia, rheumatic arthritis, rheumatoid

arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease,
asthma, chronic

obstructive pulmonary disease, osteoporosis, hypereosinophilic syndrome, mastocytosis or mast cell leukemia.

- 5 10. The compound of formula (IIa), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, or the pharmaceutical composition of claim 5 for use as a medicament for treating ovarian cancer, pancreatic cancer, prostate cancer, breast cancer, cervical cancer, glioblastoma, multiple myeloma, metabolic disease, neurodegenerative disease, primary tumor site metastasis or osseous metastasis cancer.