

BIARYL DERIVATIVE, PREPARATION METHOD THEREFOR AND PHARMACEUTICAL USE THEREOF

TECHNICAL FIELD

The present invention belongs to the field of pharmaceutical synthesis, and particularly relates to a biaryl derivative, a preparation method therefor and a pharmaceutical use thereof.

BACKGROUND

5 The immune system plays a very important role in controlling and eliminating diseases, such as cancer. However, tumor cells are often able to develop a strategy for escaping or suppressing the monitoring of the immune system to promote their malignant growth. One very important mechanism is to change the expression of co-stimulatory and co-inhibitory immune checkpoint molecules on immunocytes. Blocking the signal
10 pathway of immune checkpoint molecules, such as PD1, has been proved to be an extremely promising and effective therapy.

Programmed cell death protein 1 (PD-1), also known as CD279, is a receptor expressed on the surfaces of activated T cells, natural killer T cells, B cells and macrophages. The structure of PD-1 contains an extracellular domain similar to an
15 immunoglobulin variable region, a transmembrane domain and an intracellular domain, wherein the intracellular domain contains two phosphorylation sites located in an immunoreceptor tyrosine kinase-based inhibitory domain and an immunoreceptor tyrosine kinase-based transduction domain, suggesting that PD1 can down-regulate T cell receptor-mediated signal pathways.

20 PD1 has two ligands: PD-L1 and PDL2, and they are different in their expression profile. The expression of PDL1 will be up-regulated in macrophages and dendritic cells after treatment with lipopolysaccharide (LPS) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and will also be up-regulated in T cells and B cells after stimulation of T cell receptor and B cell receptor signal pathways. PD-L1 is also highly
25 expressed in almost all tumor cells, and the expression will be up-regulated after stimulation of interferon (IFN) gamma. As a matter of fact, the expression of PDL1 in a variety of tumors is considered to have prognostic relevance, but the expression of PD-L2 is relatively concentrated, and mainly on dendritic cells.

When T cells expressing PD-1 come into contact with cells expressing the ligands
30 of PD-1, those antigen-stimulated functional activities, such as cell proliferation, cytokine release and cell lysis activity, are all inhibited. Therefore, the interaction between PD1 and its ligands thereof can function as an intrinsic negative feedback regulation mechanism to prevent T cell hyperactivation during infection, immune tolerance or tumorigenesis, thus reducing the occurrence of autoimmune diseases and promoting self
35 tolerance. Long-term antigen stimulation, e.g., in tumor or long-term infection, will cause

T cells to express high level of PD-1, gradually lose activities in response to these long-term antigens, and eventually become nonfunctional, namely, the so-called T cell exhaustion. B cells also have the inhibitory effect caused by PD1 and ligands thereof and corresponding functional exhaustion.

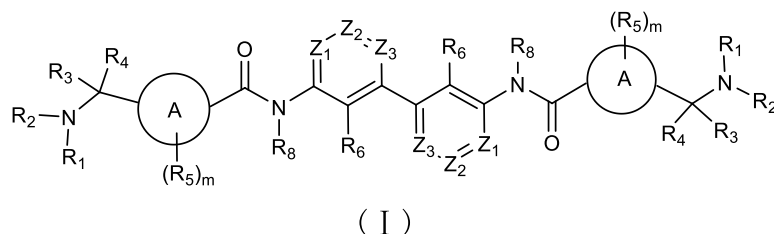
Some evidence from preclinical animal studies have indicated that PD-1 and its ligands thereof can down-regulate the immunoreaction. PD-1-deficient mice will develop lupus erythematosus-like acute proliferative glomerulonephritis and dilated cardiomyopathy. Utilizing the antibody of PDL1 to block the interaction between PD-1 and PDL1 has been proved to be able to restore and enhance T cell activation in many systems. The monoclonal antibody of PDL1 can also benefit patients with advanced cancers. In some preclinical animal tumor models, it was also shown that blocking the signal pathway of PD-1/PD-L1 with a monoclonal antibody can enhance the immunoreaction and lead to immunoreactions to a series of histologically different tumors. With the long-term infection LCMV model, the interaction between PD-1 and PD-L1 has been found to be able to inhibit the activation and proliferation of virus-specific CD8 T cells and the acquisition of effector cell functions. Besides being capable of enhancing the immunoreaction to long-term antigens, blocking the pathway of PD-1/PDL1 was also discovered to be able to enhance response to vaccines, including response to a therapeutic vaccine in long-term infection.

To sum up, if, besides the existing monoclonal antibody, a compound for blocking the interaction between PD1 and PDL1 can be developed, it can serve as an effective therapeutic means for blocking the PD-1/PDL1-mediated inhibitory signal pathway to enhance or restore the function of T cells. Therefore, the compound specifically blocking the interaction between PD-1 and PD-L1 will achieve a good therapeutic effect in immunotherapies for a variety of cancers and other immunity-associated diseases.

SUMMARY

The object of the present invention is to provide compounds for blocking the interaction between PD-1 and PD-L1, and thus to develop a new generation of PD-1/PD-L1 inhibitors.

The first aspect of the present invention provides a compound of formula (I), a stereoisomer, prodrug or pharmaceutically acceptable salt thereof:



wherein ring A is 5-7 membered aromatic ring or 5-7 membered heteroaromatic ring;
Z₁, Z₂ and Z₃ are each independently C(R₁₁) or N;

R₁ and R₂ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl C₁₋₈ alkyl, 3-10 membered heterocyclyl, 3-10 membered heterocyclyl C₁₋₈ alkyl, C₅₋₁₀ aryl, C₅₋₁₀ aryl C₁₋₈ alkyl and 5-10 membered heteroaryl, or, R₁ and R₂, together with the nitrogen atom directly attached thereto, form 3-10 heterocyclyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, =O, -C₀₋₈-S(O)(=N-R₇)R₉, -C₀₋₈-N=S(O)R₉R₁₀, -C₀₋₈-N=SR₉R₁₀, -C₀₋₈-P(O)(OH)R₁₂, -C₀₋₈-SF₅, -C₀₋₈-O-S(O)₂R₁₂, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

R₃ and R₄ are each independently selected from the group consisting of hydrogen, deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄, or, R₃ and R₄, together with the carbon atom directly attached thereto, form 3-10 membered cycloalkyl or 3-10 membered heterocyclyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

R₅ is selected from the group consisting of hydrogen, deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)(=N-R₇)R₉, -C₀₋₈-N=S(O)R₉R₁₀, -C₀₋₈-N=SR₉R₁₀, -C₀₋₈-P(O)(OH)R₁₂, -C₀₋₈-SF₅, -C₀₋₈-O-S(O)₂R₁₂, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄, above groups are optionally more further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered

heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

R₆ is selected from the group consisting of hydrogen, deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

R₇ is selected from the group consisting of hydrogen, deuterium, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄ and -C₀₋₈-C(O)NR₁₅R₁₆, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

each R₈ is independently selected from the group consisting of hydrogen, deuterium, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄ and -C₀₋₈-C(O)NR₁₅R₁₆, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl and 5-10 membered heteroaryl, or, R₉ and R₁₀, together with the sulfur atom directly attached thereto, form 3-10 membered heterocyclyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-

C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

each R₁₁ is independently selected from the group consisting of hydrogen, deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₄, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄;

each R₁₂ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, halogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ 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 -NR₁₅R₁₆, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, carbonyl, C₁₋₁₀ alkyl, C₁₋₁₀ 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 -NR₁₅R₁₆;

each R₁₃ is independently selected from the group consisting of hydrogen, deuterium, C₁₋₁₀ alkyl, C₂₋₁₀ 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, C₁₋₁₀ alkyl, C₁₋₁₀ 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 -NR₁₅R₁₆;

each R₁₄ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl, C₂₋₁₀ 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 -NR₁₅R₁₆, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, cyano, C₁₋₁₀ alkyl, C₁₋₁₀ 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 -NR₁₅R₁₆;

R₁₅ and R₁₆ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkoxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl,

3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, sulfinyl, sulfonyl, methanesulfonyl, isopropylsulfonyl, cyclopropylsulfonyl, *p*-toluenesulfonyl, aminosulfonyl, dimethylaminosulfonyl, amino, monoalkylamino, dialkylamino and C₁₋₁₀ alkanoyl, above groups are optionally further substituted by one or more substituents
5 selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₁₋₁₀ 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 C₁₋₁₀ alkanoyl; or,

10 R₁₅ and R₁₆, together with the nitrogen atom directly attached thereto, form 4-10 membered heterocyclyl or 4-10 membered heteroaryl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered
15 heterocyclyl, 3-10 membered heterocyclyloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy, amino, monoalkylamino, dialkylamino and C₁₋₁₀ alkanoyl;

each m is 0, 1, 2 or 3; and

each r is 0, 1 or 2.

20 As a preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, Z₁, Z₂ and Z₃ are each independently C(R₁₁) or N;

each R₁₁ is independently selected from the group consisting of hydrogen, deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, 3-8 membered
25 heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, above groups are optionally further substituted by one or more substituents selected from the group
30 consisting of deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, and R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ and r are defined as those in the compound of formula (I).

35 As a further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, Z₁, Z₂ and Z₃ are each C(R₁₁) or N; each R₁₁ is independently selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, 3-oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl, diazole, triazole, methanesulfonyl,
40 aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxy, amino, dimethylamino,

aminoacyl and acetylamino, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino.

5 As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, Z₁, Z₂ and Z₃ are each C(R₁₁) or N; each R₁₁ is independently selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, cyclopropyl, phenyl, pyridyl, diazole, triazole and methoxy, above groups are optionally further substituted by one or more
10 substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino.

As a preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₆ is selected from the group
15 consisting of hydrogen, deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, above groups are optionally further substituted by one or more substituents
20 selected from the group consisting of deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, wherein R₁₂, R₁₃,
25 R₁₄, R₁₅, R₁₆ and r are defined as those in the compound of formula (I).

As a further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₆ is selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, 3-oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl,
30 diazole, triazole, methanesulfonyl, aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxy, amino, dimethylamino, aminoacyl and acetylamino, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino.

35 As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₆ is selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, ethyl, isopropyl, trideuteriomethyl, trifluoromethyl, difluoromethyl, cyanomethyl, aminomethyl, cyclopropylmethyl, methoxymethyl, vinyl, ethynyl, cyclopropyl, cyclobutyl, 3-

oxacyclobutyl, 3-azacyclobutyl, methoxy, trideuteriomethoxy, difluoromethoxy and trifluoromethoxy.

As a preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₃ and R₄ are each independently selected from the group consisting of hydrogen, deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, or, R₃ and R₄, together with the carbon atom directly attached thereto, form 3-8 membered cycloalkyl or 3-8 membered heterocyclyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, wherein R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ and r are defined as those in the compound of formula (I).

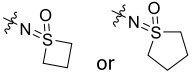
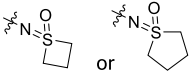
As a further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₃ and R₄ are each independently selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, 3-oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl, diazole, triazole, methanesulfonyl, aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxy, amino, dimethylamino, aminoacyl and acetylamino, or, R₃ and R₄, together with the carbon atom directly attached thereto, form 3-6 membered cycloalkyl or 3-6 membered heterocyclyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino.

As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₃ and R₄ are each independently selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, cyclopropyl, phenyl, pyridyl, diazole, triazole and methoxy, or, R₃ and R₄, together with the carbon atom directly attached thereto, form cyclopropyl, cyclobutyl, 3-oxacyclobutyl or 3-azacyclobutyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino.

As a preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₅ is selected from the group consisting of hydrogen, deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl,

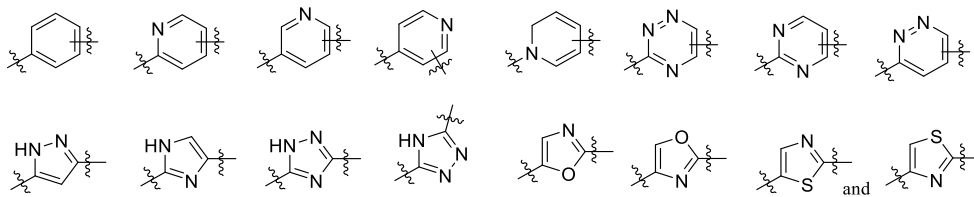
C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)(=N-R₇)R₉, -C₀₋₄-N=S(O)R₉R₁₀, -C₀₋₄-N=SR₉R₁₀, -C₀₋₄-P(O)(OH)R₁₂, -C₀₋₄-SF₅, -C₀₋₄-O-S(O)₂R₁₂, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, -C₀₋₄-S(O)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, above groups are optionally more further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, 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)_rR₁₂, -C₀₋₄-O-R₁₃, -C₀₋₄-C(O)OR₁₃, -C₀₋₄-C(O)R₁₄, -C₀₋₄-O-C(O)R₁₄, -C₀₋₄-NR₁₅R₁₆, -C₀₋₄-C(=NR₁₅)R₁₄, -C₀₋₄-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₄-C(O)NR₁₅R₁₆ and -C₀₋₄-N(R₁₅)-C(O)R₁₄, wherein R₇, R₉, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ and r are defined as those in the compound of formula (I).

As a further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₅ is selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, ethyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, 3-oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl, diazole, triazole, -SF₅, -S(O)(=NH)CH₃, -N=S(O)(CH₃)₂, -N=S(CH₃)₂, -C₀₋₄-P(O)(OH)F, -O-S(O)₂F, fluorosulfonyl, methanesulfonyl, aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxyl, amino, dimethylamino, aminoacyl, acetylamino and the

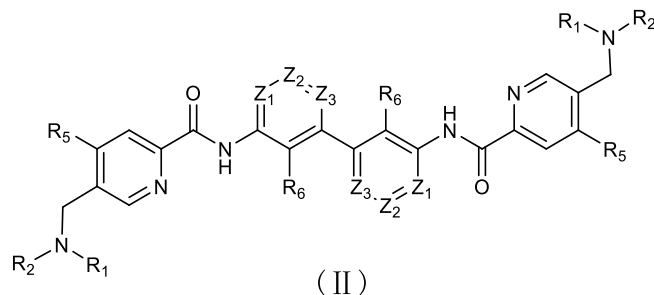
following structure:  or , above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, diazole, triazole, methanesulfonyl, aminosulfonyl, methoxy and amino, above groups are optionally more further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, aminosulfonyl, methoxy and amino.

As a further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, ring A is 5-6 membered aromatic ring or 5-6 membered heteroaromatic ring.

As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, ring A is selected from the following group consisting of:



As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, the compound of formula (I) is a compound with the structure shown as formula (II):

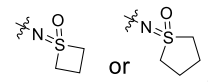


(II)

wherein, Z_1 , Z_2 and Z_3 are each independently $C(R_{11})$;

R_5 is selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, ethyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, 3-oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl, diazole, triazole, $-SF_5$, $-S(O)(=NH)CH_3$, $-N=S(O)(CH_3)_2$, $-N=S(CH_3)_2$, $-C_{0-4}-P(O)(OH)F$, $-O-S(O)_2F$, fluorosulfonyl, methanesulfonyl, aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxy, amino,

dimethylamino, aminoacyl, acetylamino and the following structure:



above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, diazole, triazole, methanesulfonyl, aminosulfonyl, methoxy and amino, above groups are optionally more further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, aminosulfonyl, methoxy and amino;

R_6 is selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, ethyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, 3-oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl, diazole, triazole, methanesulfonyl, aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxy, amino, dimethylamino, aminoacyl and acetylamino, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino;

each R_{11} is independently selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, 3-

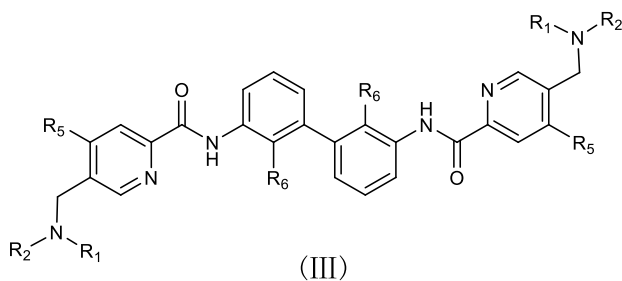
oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl, diazole, triazole, methanesulfonyl, aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxy, amino, dimethylamino, aminoacyl and acetylamino, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino; and

R₁ and R₂ are as defined as those in the compound of formula (I).

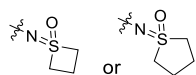
As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₆ is selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, ethyl, isopropyl, trideuteriomethyl, trifluoromethyl, difluoromethyl, cyanomethyl, aminomethyl, cyclopropylmethyl, methoxymethyl, vinyl, ethynyl, cyclopropyl, cyclobutyl, 3-oxacyclobutyl, 3-azacyclobutyl, methoxy, trideuteriomethoxy, difluoromethoxy and trifluoromethoxy; and

each R₁₁ is independently selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, cyclopropyl, phenyl, pyridyl, diazole, triazole and methoxy, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, methoxy and amino.

As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, the compound of formula (I) is a compound with the structure shown as formula (III):



wherein, R₆ is selected from the group consisting of deuterium, chlorine, fluorine, methyl, cyano, trideuteriomethyl, cyanomethyl, aminomethyl, cyclopropylmethyl, methoxymethyl and cyclopropyl; R₅ is selected from the group consisting of hydrogen, deuterium, fluorine, chlorine, cyano, methyl, ethyl, isopropyl, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, 3-oxacyclobutyl, 3-azacyclobutyl, phenyl, pyridyl, diazole, triazole, -SF₅, -S(O)(=NH)CH₃, -N=S(O)(CH₃)₂, -P(O)(OH)F, -O-S(O)₂F, -N=S(CH₃)₂, fluorosulfonyl, methanesulfonyl, aminosulfonyl, methoxy, methoxyacyl, acetyl, acetoxy, amino, dimethylamino, aminoacyl, acetylamino and the following structure:

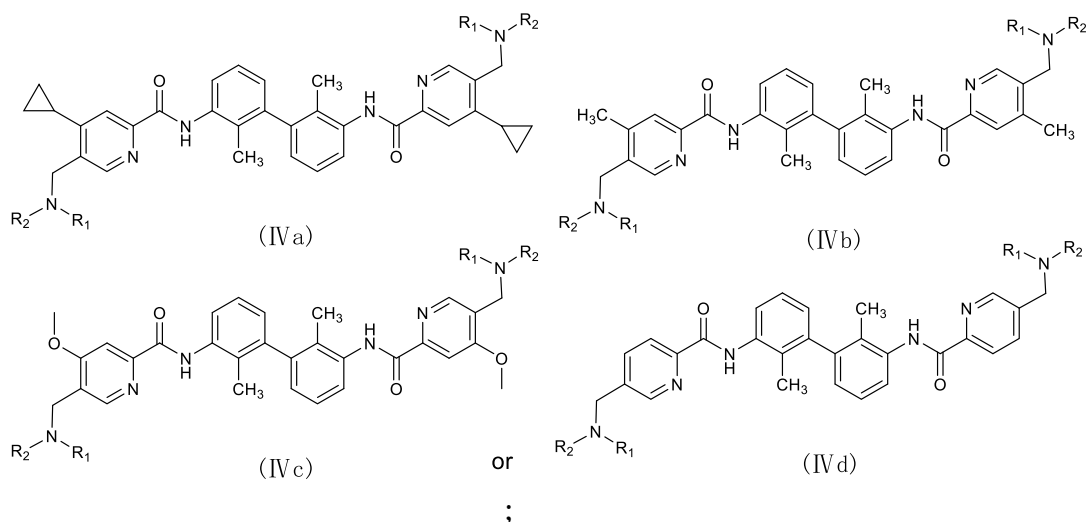


, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano,

methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, diazole, triazole, methanesulfonyl, aminosulfonyl, methoxy or amino, above groups are optionally more further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, methyl, trifluoromethyl, cyclopropyl, phenyl, pyridyl, methanesulfonyl, aminosulfonyl, methoxy and amino; and

R_1 and R_2 are defined as those in the compound of formula (I).

As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, the compound of formula (I) is a compound with the structure shown as formula (IVa), formula (IVb), formula (IVc) or formula (IVd):



wherein, R_1 and R_2 are each independently defined as those in the compound of formula (I).

As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R_1 and R_2 are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, 3-8 membered heterocyclyl, C_{5-8} aryl and 5-8 membered heteroaryl, or, R_1 and R_2 , together with the nitrogen atom directly attached thereto, form 3-8 membered heterocyclyl, the heteroatom in the heterocyclyl is selected from the group consisting of N, O, S and/or Si, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} deuterioalkyl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, C_{5-8} aryl, 5-8 membered heteroaryl, $=O$, $-S(O)(=N-R_7)R_9$, $-N=S(O)R_9R_{10}$, $-N=SR_9R_{10}$, $-P(O)(OH)R_{12}$, $-SF_5$, $-O-S(O)_2R_{12}$, $-S(O)_rR_{12}$, $-O-R_{13}$, $-C(O)OR_{13}$, $-C(O)R_{14}$, $-O-C(O)R_{14}$, $-NR_{15}R_{16}$, $-C(=NR_{15})R_{14}$, $-N(R_{15})-C(=NR_{16})R_{14}$, $-C(O)NR_{15}R_{16}$ and $-N(R_{15})-C(O)R_{14}$; and

R_7 , R_9 , R_{10} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} and r are defined as those in the compound of formula (I).

As a more further preferred embodiment, in the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, R₁ is hydrogen, deuterium or methyl; R₂ is selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl and 5-8 membered heteroaryl, or, R₁ and R₂, together with the nitrogen atom directly attached thereto, form 3-8 membered heterocyclyl, the heteroatom in the heterocyclyl is selected from the group consisting of N, O, S and/or Si, 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, C₁₋₄ deuterioalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, =O, -S(O)(=N-R₇)R₉, -N=S(O)R₉R₁₀, -N=SR₉R₁₀, -P(O)(OH)R₁₂, -SF₅, -O-S(O)₂R₁₂, -S(O)_rR₁₂, -O-R₁₃, -C(O)OR₁₃, -C(O)R₁₄, -O-C(O)R₁₄, -NR₁₅R₁₆, -C(=NR₁₅)R₁₄, -N(R₁₅)-C(=NR₁₆)R₁₄, -C(O)NR₁₅R₁₆ and -N(R₁₅)-C(O)R₁₄;

R₇ is selected from the group consisting of hydrogen, deuterium, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl, methanesulfonyl and acetyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, hydroxy, methyl, ethyl, trifluoromethyl, difluoromethyl, trideuteriomethyl, dideuteriomethyl, cyclopropyl, phenyl, diazole, triazole, methoxy, ethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, acetyl, acetoxo, amino and dimethylamino;

R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl and 5-8 membered heteroaryl, or, R₉ and R₁₀, together with the sulfur atom directly attached thereto, form 3-6 membered heterocyclyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, hydroxy, methyl, ethyl, trifluoromethyl, difluoromethyl, trideuteriomethyl, dideuteriomethyl, cyclopropyl, phenyl, diazole, triazole, methoxy, ethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, acetyl, acetoxo, amino and dimethylamino;

each R₁₂ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, halogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl and -NR₁₅R₁₆, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, hydroxy, carbonyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl, amino and dimethylamino;

each R₁₃ is independently selected from the group consisting of hydrogen, deuterium, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl and 5-8 membered heteroaryl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, carbonyl, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered

heterocyclyl, 3-6 membered heterocyclyloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy and -NR₁₅R₁₆;

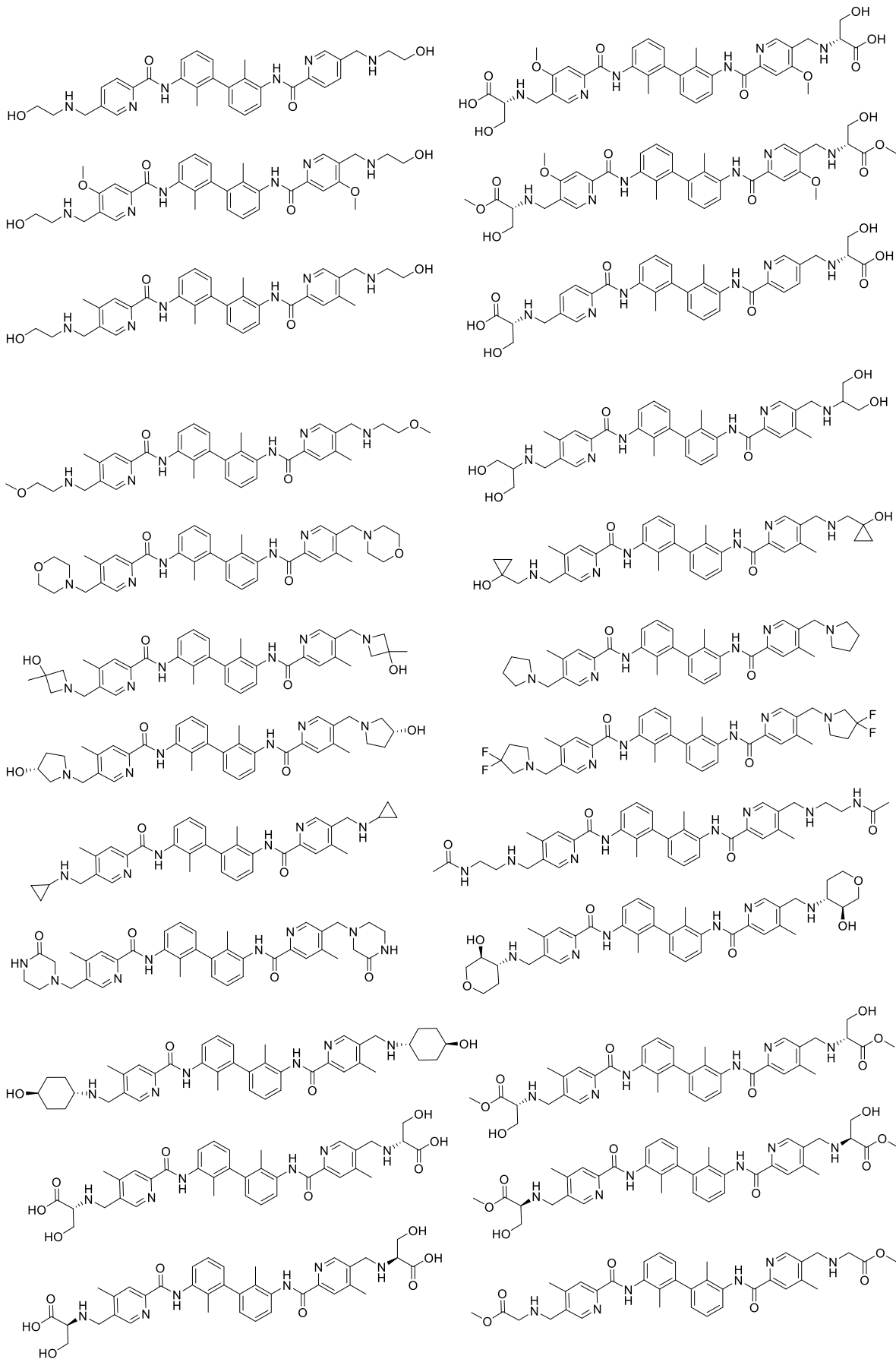
each R₁₄ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocyclyloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy and -NR₁₅R₁₆, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocyclyloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy and -NR₁₅R₁₆;

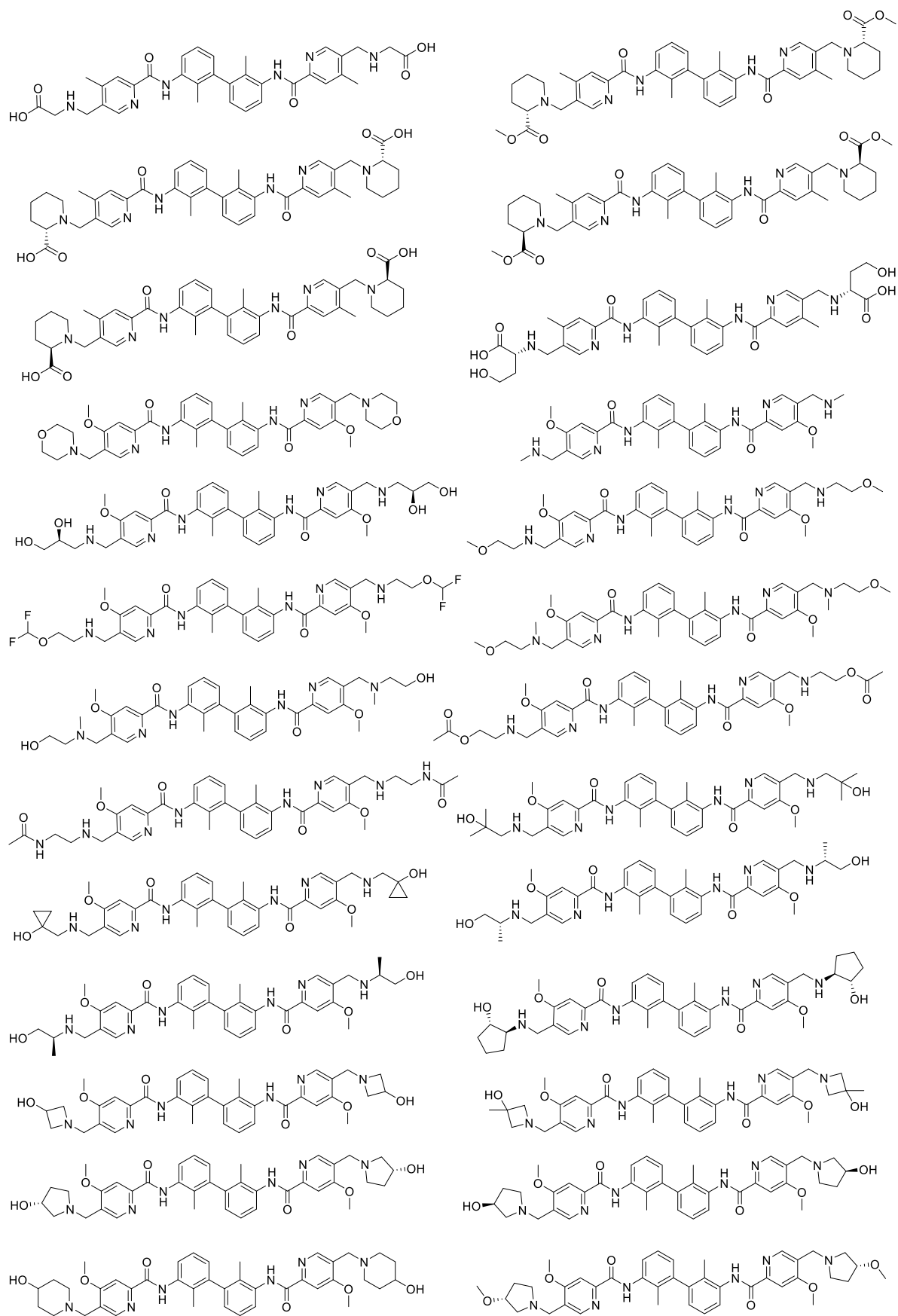
each of R₁₅ and R₁₆ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl, sulfinyl, sulfonyl, methanesulfonyl, isopropylsulfonyl, cyclopropylsulfonyl, *p*-toluenesulfonyl, aminosulfonyl, dimethylaminosulfonyl, amino, monoalkylamino, dialkylamino and C₁₋₄ alkanoyl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocyclyloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy, amino, monoalkylamino, dialkylamino and C₁₋₄ alkanoyl; or,

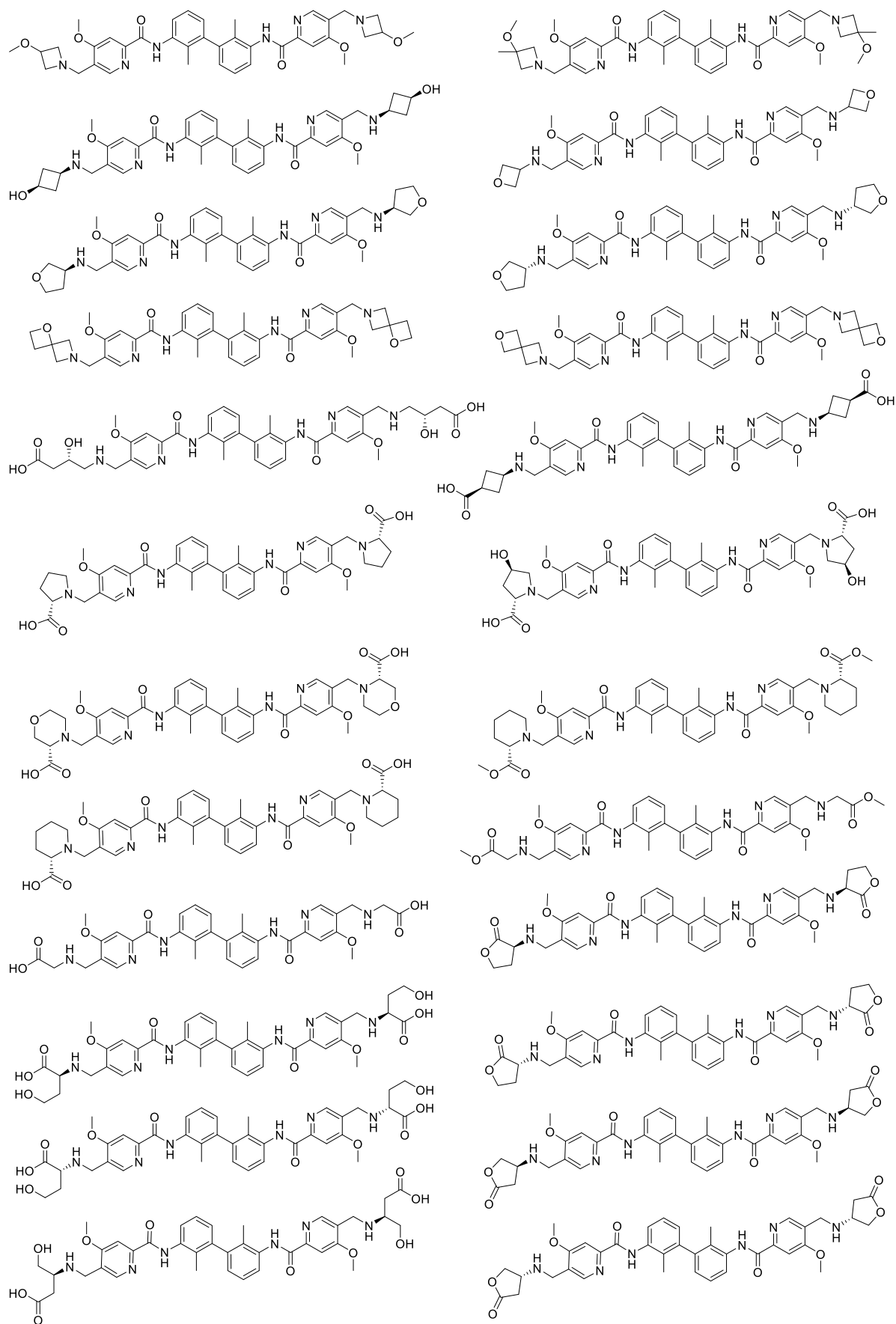
R₁₅ and R₁₆, together with the nitrogen atom directly attached thereto, form 4-6 membered heterocyclyl or 4-6 membered heteroaryl, above groups are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocyclyloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy, amino, monoalkylamino, dialkylamino and C₁₋₄ alkanoyl; and

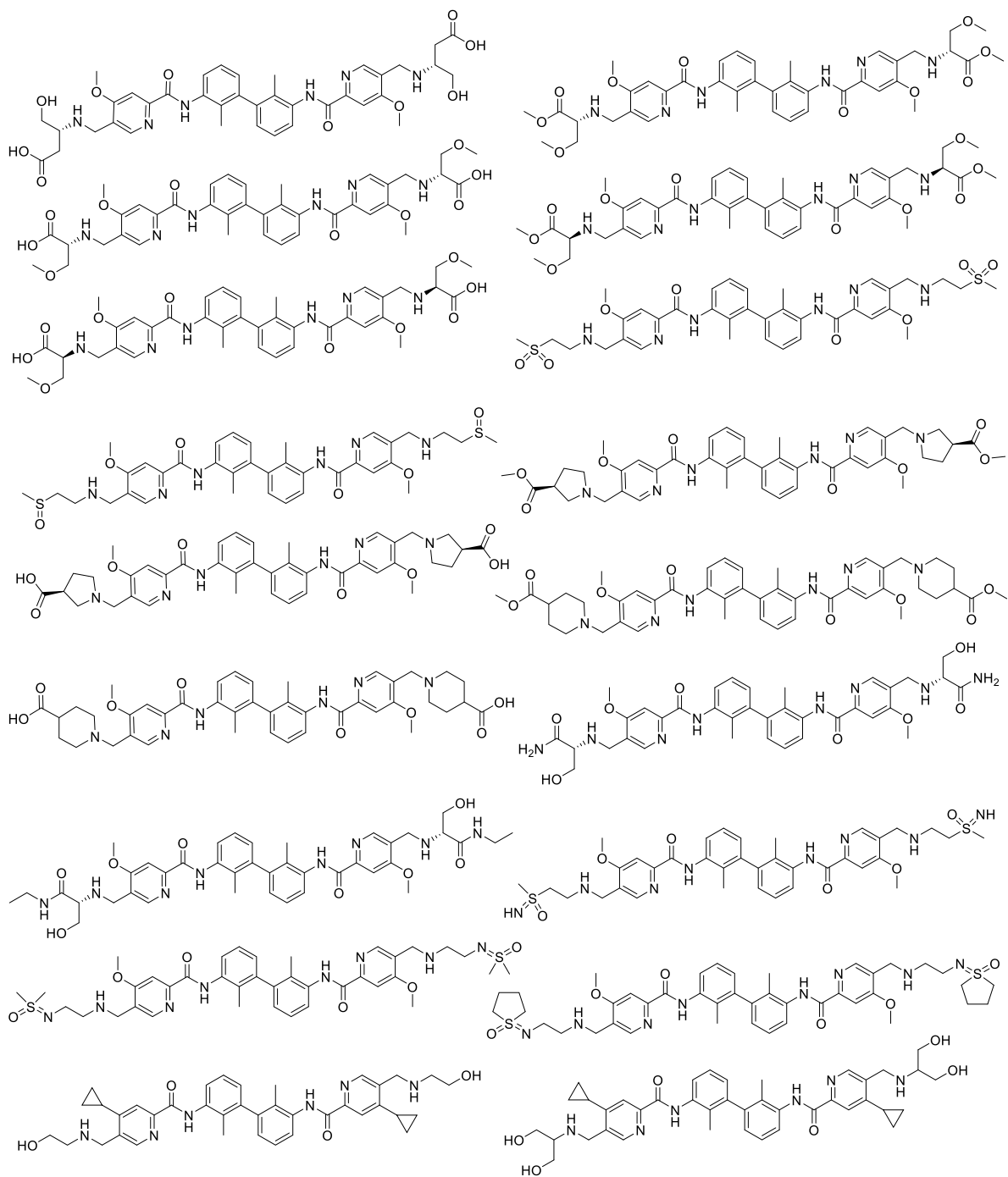
r is independently 0, 1 or 2.

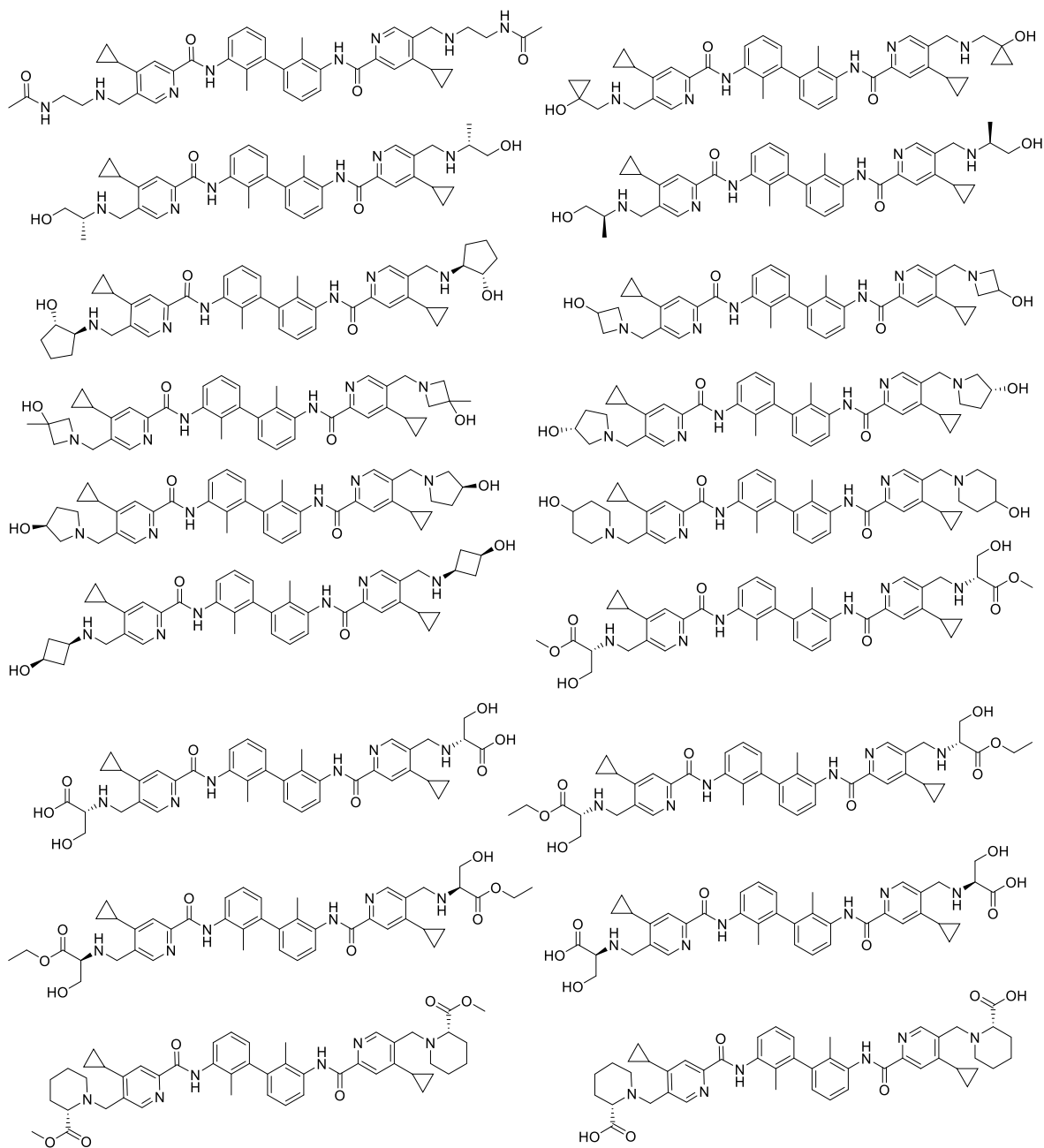
As the most preferred embodiment, the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof include, but are not limited to, the following compounds:

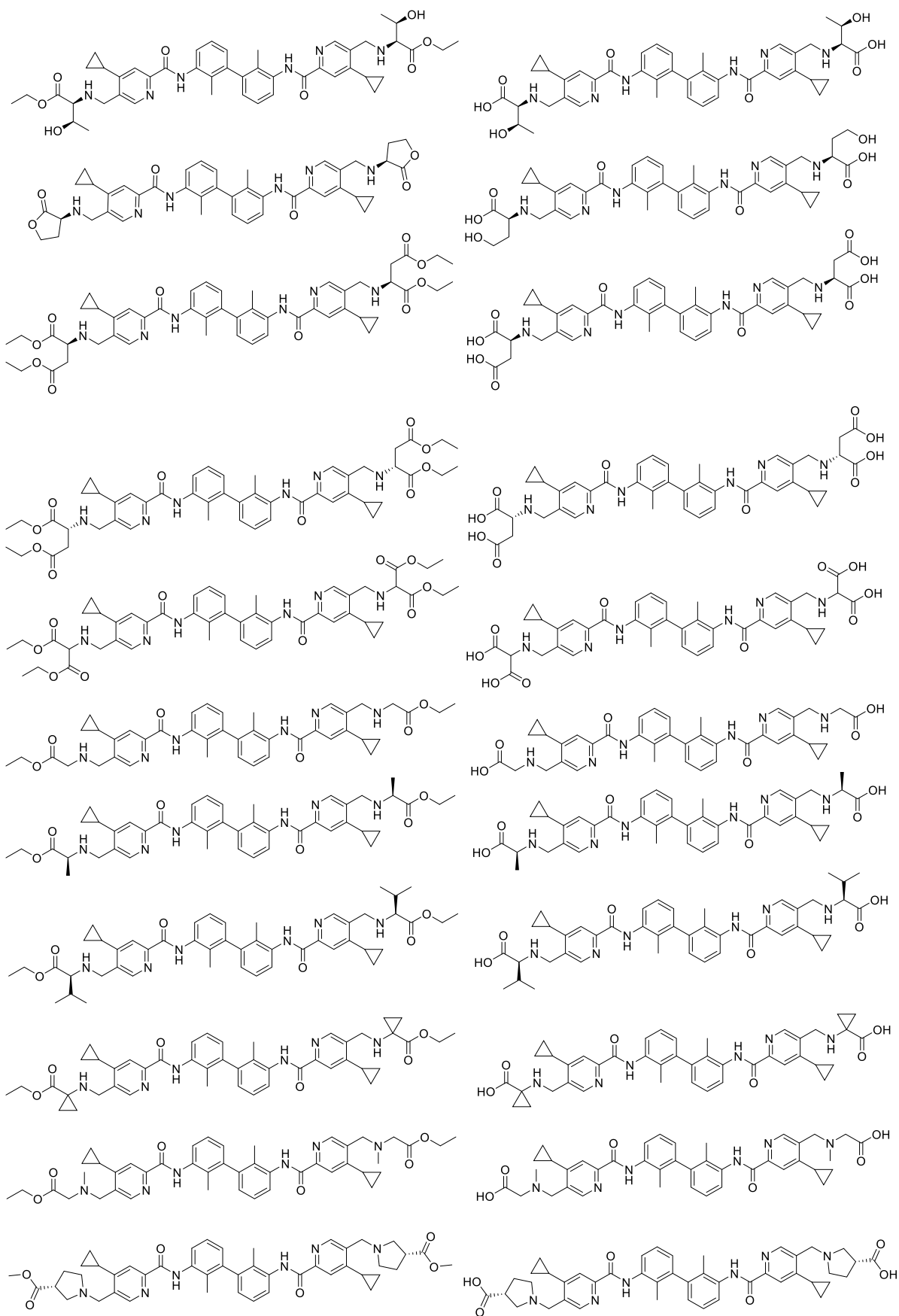


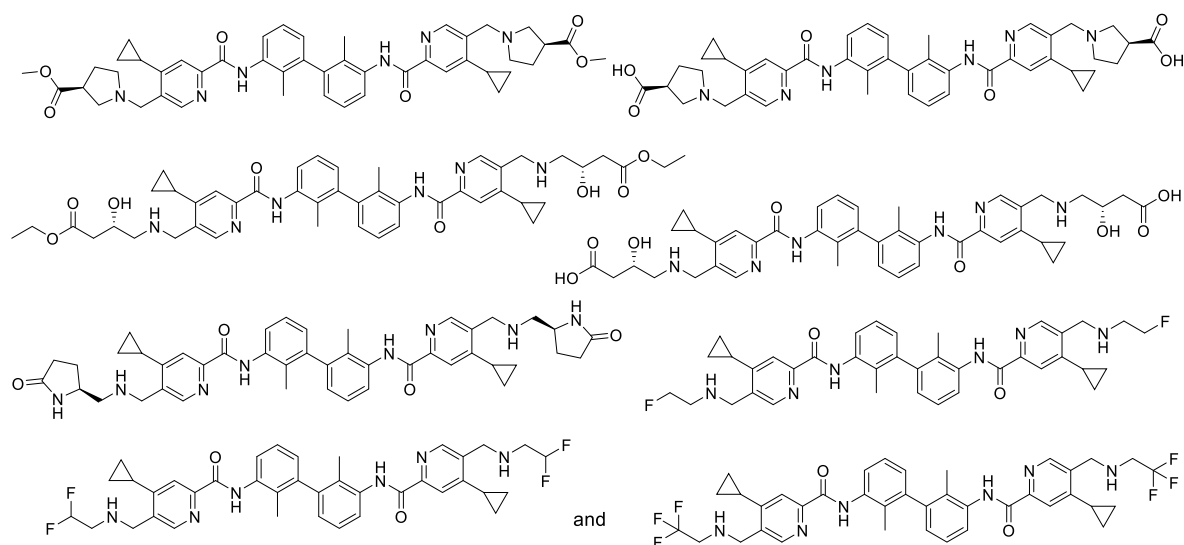




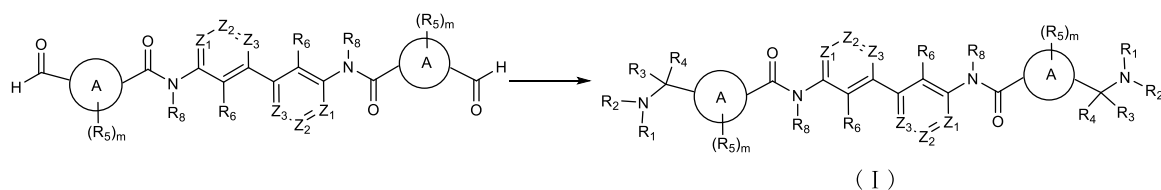








The second aspect of the present invention provides a process for preparing the compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, comprising the following steps:



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wherein ring A, Z₁, Z₂, Z₃, R₁, R₂, R₃, R₄, R₅, R₆, R₈ and m are defined as those in the compound of formula (I).

The third aspect of the present invention provides a pharmaceutical composition, comprising the aforementioned compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The fourth aspect of the present invention provides a use of the aforementioned compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition in the preparation of a medicament for preventing and/or treating PD-1/PD-L1 signal pathway-mediated disease.

As a preferred embodiment, the aforementioned PD-1/PD-L1 signal pathway-mediated disease is cancer or tumor, immune-related disease and disorder, communicable disease, infectious disease and metabolic disease.

As a further preferred embodiment, the aforementioned infectious disease is bacterial infectious disease, viral infectious disease or fungal infectious disease.

As a further preferred embodiment, the aforementioned cancer or tumor is selected from lymphoma (including but not limited to lymphocytic lymphoma, primary central nervous system lymphoma, T cell lymphoma, diffuse large B cell lymphoma, follicle center lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma or primary mediastinal large B cell lymphoma), sarcoma (including but not limited to Kaposi's sarcoma,

fibrosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, leiomyosarcoma, rhabdomyosarcoma, soft tissue sarcoma, angiosarcoma or lymphangiosarcoma), melanoma, glioblastoma, synovioma, meningioma, biliary tract tumor, thymic tumor, neuroma, seminoma, nephroblastoma, pleomorphic adenoma, hepatocellular papilloma, renal tubule adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma, fibroma, central nervous system tumor, rhachiophyma, brain stem glioma, pituitary adenoma, multiple myeloma, ovarian tumor, myelodysplastic syndrome or mesothelioma, prostate cancer, recurrent prostate cancer or prostate cancer having developed resistance to existing medicaments, thyroid cancer, parathyroid cancer, anal cancer, testicular cancer, urethral carcinoma, penile cancer, bladder cancer, ureteral cancer, uterine cancer, ovarian cancer, fallopian tube cancer, endometrial cancer, cervical cancer, vaginal cancer, vulvar cancer, adrenal cancer, Merkel cell carcinoma, embryonal carcinoma, chronic or acute leukemia (including but not limited to acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic granulocytic leukemia and chronic lymphoblastic leukemia), bronchial carcinoma, esophageal cancer, nasopharyngeal carcinoma, hepatocellular carcinoma, renal cell carcinoma, small cell lung cancer, basal cell carcinoma, lung cancer, breast cancer, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, squamous non-small cell lung cancer, non-squamous non-small cell lung cancer, rectal cancer, colon cancer, colorectal cancer, gastric cancer, pancreatic cancer, head and neck squamous cell carcinoma, head and neck cancer, gastrointestinal cancer, bone cancer, skin cancer, small intestine cancer, endocrine cancer, renal pelvic carcinoma, epidermoid carcinoma, abdominal wall carcinoma, renal cell carcinoma, transitional cell carcinoma, choriocarcinoma, or metastatic tumor, especially metastatic tumor expressing PD-L1.

As a further preferred embodiment, the aforementioned immune-related disease and disorder is selected from rheumatic arthritis, renal failure, lupus erythematosus, asthma, psoriasis, ulcerative colitis, pancreatitis, allergy, fibrosis, anemia, fibromyalgia, Alzheimer's disease, congestive heart failure, stroke, aortic valve stenosis, arteriosclerosis, osteoporosis, Parkinson's disease, infection, Crohn's disease, ulcerative colitis, allergic contact dermatitis and eczema, systemic sclerosis or multiple sclerosis.

As a further preferred embodiment, the aforementioned communicable disease or infectious disease is selected from sepsis, liver infection, HIV, hepatitis A, hepatitis B, hepatitis C, hepatitis D, herpes virus, papillomavirus or influenza.

As a further preferred embodiment, the aforementioned metabolic disease is selected from diabetes, diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, hypoglycemia, gout, malnutrition, vitamin A deficiency, scurvy, vitamin D deficiency or osteoporosis.

The fifth aspect of the present invention provides the aforementioned compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof or the

aforementioned pharmaceutical composition for use as a medicament for preventing and/or treating PD-1/PD-L1 signal pathway-mediated cancer or tumor, immune-related disease and disorder, communicable disease, infectious disease or metabolic disease.

The sixth aspect of the present invention provides a method for preventing and/or treating PD-1/PD-L1 signal pathway-mediated cancer or tumor, immune-related disease and disorder, communicable disease, infectious disease or metabolic disease, comprising administering the aforementioned compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition to a patient.

The seventh aspect of the present invention provides a method for enhancing, stimulating, regulating and/or increasing the immune response mediated by the PD-1/PD-L1 signal pathway in a subject in need, comprising administering the aforementioned compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition to a patient.

The eighth aspect of the present invention provides a method for inhibiting the growth, proliferation or metastasis of tumor cells, comprising administering the aforementioned compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition to a patient.

The ninth aspect of the present invention provides a method for treating PD-1/PD-L1 signal pathway-mediated communicable disease, infectious disease, metabolic disease or disorder, comprising administering the aforementioned compound of formula (I), the stereoisomer, prodrug or pharmaceutically acceptable salt thereof or the aforementioned pharmaceutical composition to a patient.

DETAILED DESCRIPTION OF THE INVENTION

After an extensive and intensive research, the inventors of the present invention, for the first time, developed a series of compounds of general formula (I) that are globally symmetrical but have some differences locally in structure, and in particular the compounds of a fully symmetrical structure, and the series of compounds are biaryl derivatives for inhibiting the interaction between PD-1 and PD-L1. With a strong inhibitory effect on the interaction between PD-1 and PD-L1, the series of compounds of the present invention can be widely applied in the preparation of medicaments for preventing and/or treating cancer or tumor, immune-related disease and disorder, communicable disease, infectious disease or metabolic disease that is mediated by the PD-1/PD-L1 signal pathway, and are expected to be developed into a new generation of PD-1/PD-L1 inhibitors. The present invention is achieved on this basis.

Detailed description: Unless otherwise stated, the following terms used in the specification and claims have the following meanings.

"Alkyl" refers to linear or branched saturated aliphatic alkyl groups, for example, "C₁₋₁₀ alkyl" means a linear or branched alkyl containing 1 to 10 carbon atoms, which

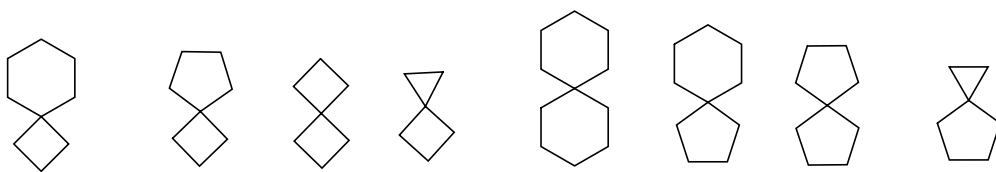
includes, but is not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, *n*-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylpentyl, *n*-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, *n*-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl or various branched isomers thereof, etc.

Alkyl may be optionally substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"Cycloalkyl" or "carbocycle" refers to a monocyclic or polycyclic hydrocarbon substituent that is saturated or partially unsaturated, for example, "C₃₋₁₀ cycloalkyl" means a cycloalkyl containing 3 to 10 carbon atoms, which may be monocyclic cycloalkyl and polycyclic cycloalkyl, wherein,

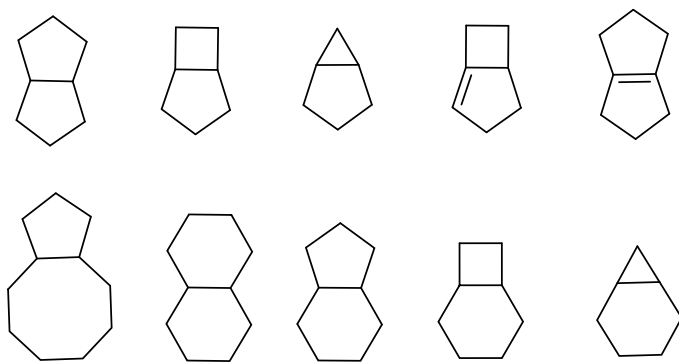
monocyclic cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl, etc.

Polycyclic cycloalkyl includes spirocycloalkyl, fused cycloalkyl and bridged cycloalkyl. "Spirocycloalkyl" refers to a polycyclic group in which a carbon atom (called spiro-atom) is shared among monocyclic rings, wherein those rings may contain one or more double bonds, but none of them has a fully conjugated π -electron system. According to the number of the spiro-atoms shared among the rings, the spirocycloalkyl may be monospirocycloalkyl, bispirocycloalkyl or polyspirocycloalkyl, including but not limited to:

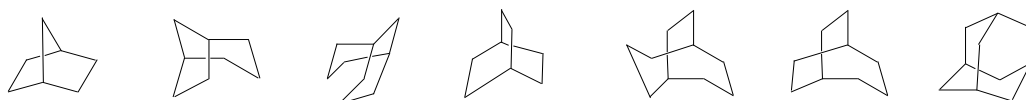


"Fused cycloalkyl" refers to an all-carbon polycyclic group in which each ring shares a pair of adjacent carbon atoms with the other rings in the system, wherein one or more of the rings may contain one or more double bonds, but none of them has a fully conjugated π -electron system. According to the number of formed rings, the fused

cycloalkyl may be bicyclic, tricyclic, tetracyclic or polycyclic, including but not limited to:



"Bridged cycloalkyl" refers to an all-carbon polycyclic group in which any two rings share two carbon atoms that are not directly connected to each other, wherein these rings may contain one or more double bonds, but none of them has a fully conjugated π -electron system. According to the number of formed rings, the bridged cycloalkyl may be bicyclic, tricyclic, tetracyclic or polycyclic, including but not limited to:



The cycloalkyl ring can be fused to an aryl, heteroaryl or heterocycloalkyl ring, wherein the ring attached to the parent structure is cycloalkyl, which includes, but is not limited to, indanyl, tetrahydronaphthyl, benzocycloheptyl, etc.

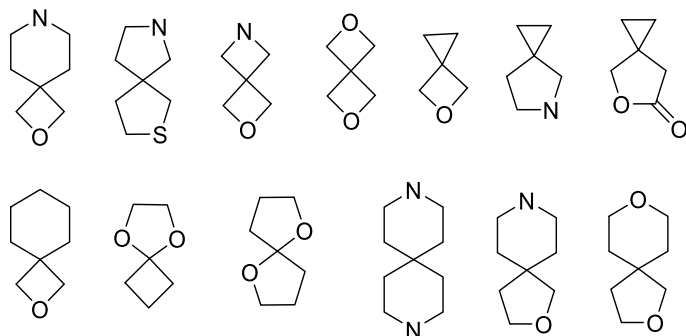
Cycloalkyl may be optionally substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} haloalkyl, C_{1-10} deuterioalkyl, C_{3-10} cycloalkyl, 3-10 membered heterocyclyl, C_{5-10} aryl, 5-10 membered heteroaryl, $-C_{0-8}-S(O)_rR_{12}$, $-C_{0-8}-O-R_{13}$, $-C_{0-8}-C(O)OR_{13}$, $-C_{0-8}-C(O)R_{13}$, $-C_{0-8}-O-C(O)R_{14}$, $-C_{0-8}-NR_{15}R_{16}$, $-C_{0-8}-C(=NR_{15})R_{14}$, $-C_{0-8}-N(R_{15})-C(=NR_{16})R_{14}$, $-C_{0-8}-C(O)NR_{15}R_{16}$ and $-C_{0-8}-N(R_{15})-C(O)R_{14}$.

"Heterocyclyl" or "heterocyclic ring" refers to a monocyclic or polycyclic hydrocarbon substituent that is saturated or partially unsaturated, wherein one or more of the ring atoms are heteroatoms selected from nitrogen, oxygen, silicon or $S(O)_r$ (wherein r is an integer of 0, 1 or 2), excluding ring portions of $-O-O-$, $-O-S-$ or $-S-S-$, and the remaining ring atoms are carbon atoms. For example, "4-10 membered heterocyclyl" refers to a cyclic group containing 4 to 10 ring atoms, and "3-6 membered heterocyclyl" means a cyclic group containing 3 to 6 ring atoms.

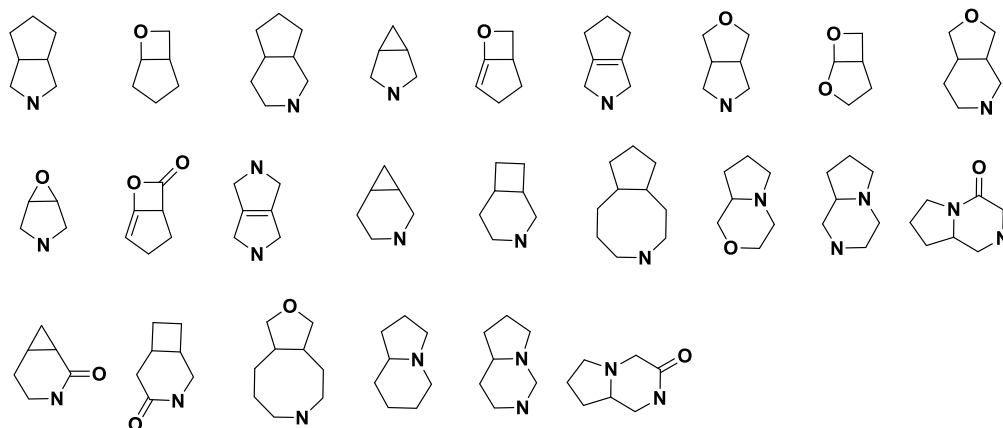
Monocyclic heterocyclyl includes, but is not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperazinyl, etc.

Polycyclic heterocyclyl includes spiroheterocyclyl, fused heterocyclyl, and bridged heterocyclyl. "Spiroheterocyclyl" refers to a polycyclic heterocyclyl group in which an atom (called spiro-atom) is shared among monocyclic rings, wherein one or more ring

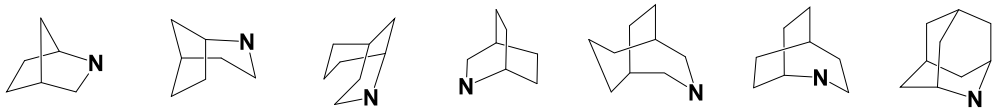
atoms are heteroatoms selected from nitrogen, oxygen, silicon or $S(O)_r$ (wherein r is an integer of 0, 1 or 2), and the remaining ring atoms are carbon atoms. These rings may contain one or more double bonds, but none of them has a fully conjugated π -electron system. According to the number of spiro-atoms shared among the rings, spiroheterocyclyl may be monospiroheterocyclyl, bispiroheterocyclyl or polyspiroheterocyclyl. Spiroheterocyclyl includes, but is not limited to:



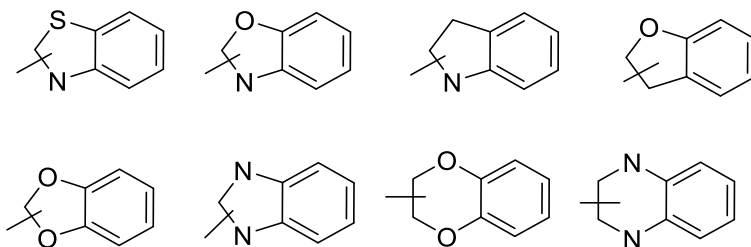
"Fused heterocyclyl" refers to a polycyclic heterocyclyl in which each ring shares a pair of adjacent atoms with the other rings in the system, wherein one or more of the rings may contain one or more double bonds, but none of them has a fully conjugated π -electron system, wherein one or more of the ring atoms are heteroatoms selected from nitrogen, oxygen, silicon or $S(O)_r$ (wherein r is an integer of 0, 1 or 2), and the remaining ring atoms are carbon atoms. According to the number of formed rings, the fused heterocyclyl may be bicyclic, tricyclic, tetracyclic or polycyclic, including, but not limited to:



"Bridged heterocyclyl" refers to a polycyclic heterocyclyl in which any two rings share two carbon atoms that are not directly attached to each other, wherein these rings may contain one or more double bonds, but none of them has a fully conjugated π -electron system, wherein one or more of the ring atoms are heteroatoms selected from nitrogen, oxygen, silicon or $S(O)_r$ (wherein r is an integer of 0, 1 or 2), and the remaining ring atoms are carbon atoms. According to the number of formed rings, the bridged heterocyclyl may be bicyclic, tricyclic, tetracyclic or polycyclic, including, but not limited to:

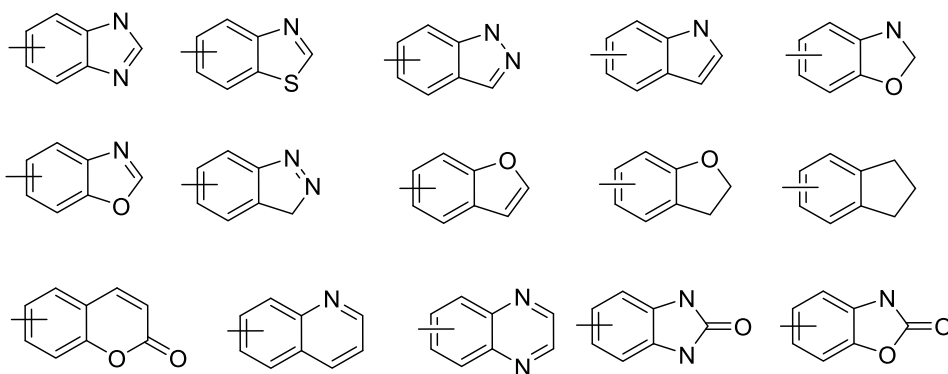


The heterocyclyl ring may be fused to an aryl, heteroaryl or cycloalkyl ring, wherein the ring attached to the parent structure is heterocyclyl, including, but not limited to:



- 5 Heterocyclyl may be optionally substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-
- 10 R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

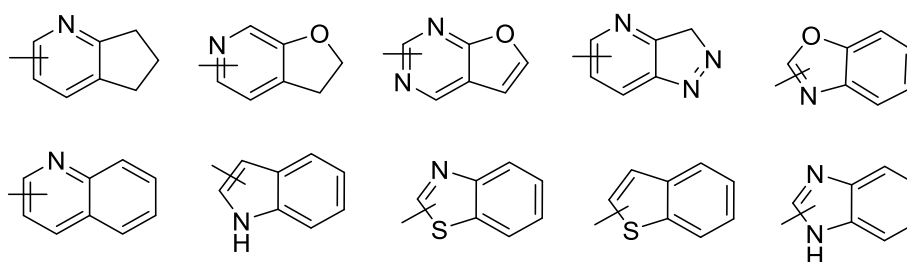
- "Aryl" or "aromatic ring" means an all-carbon monocyclic or fused-polycyclic group (i.e., rings that share a pair of adjacent carbon atoms) and a polycyclic group having a conjugated π -electron system (i.e., rings with adjacent pairs of carbon atoms), for example,
- 15 "C₅₋₁₀ aryl" means an all-carbon aryl group containing 5 to 10 carbon atoms, and "5-10 membered aryl" means an all-carbon aryl group containing 5 to 10 carbon atoms, including, but not limited to, phenyl and naphthyl. The aryl ring can be fused to a heteroaryl, heterocyclyl or cycloalkyl ring, wherein the ring attached to the parent structure is the aryl ring, including, but not limited to:



- 20 Aryl may be substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-
- 25

O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"Heteroaryl" or "heteroaromatic ring" refers to a heteroaromatic system containing 1 to 4 heteroatoms, and the heteroatoms include heteroatoms selected from nitrogen, oxygen or S(O)_r (wherein r is an integer of 0, 1 or 2), for example, 5-10 membered heteroaryl means a heteroaromatic system containing 5 to 10 ring atoms, and 5-8 membered heteroaryl means a heteroaromatic system containing 5 to 8 ring atoms, including, but not limited to, furyl, thiophenyl, pyridyl, pyrrolyl, N-alkylpyrrolyl, pyrimidinyl, pyrazinyl, imidazolyl, tetrazolyl, etc. The heteroaryl ring can be fused to an aryl, heterocyclyl or cycloalkyl ring, wherein the ring attached to the parent structure is the heteroaryl ring, including, but not limited to:



Heteroaryl may be optionally substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"Alkenyl" refers to an alkyl defined as above consisting of at least two carbon atoms and at least one carbon-carbon double bond, for example, C₂₋₁₀ alkenyl means a linear or branched alkenyl group containing 2 to 10 carbon atoms. The alkenyl includes, but is not limited to, vinyl, 1-propenyl, 2-propenyl, 1-, 2- or 3-butenyl, etc.

Alkenyl may be substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"Alkynyl" refers to an alkyl defined as above consisting of at least two carbon atoms and at least one carbon-carbon triple bond, for example, C₂₋₁₀ alkynyl means a linear or branched alkynyl group containing 2 to 10 carbon atoms. The alkynyl includes, but is not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2- or 3-butylnyl, etc.

Alkynyl may be substituted or unsubstituted, and when it is substituted, the

substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"Alkoxy" refers to -O-(alkyl), wherein the alkyl is defined as above, for example, "C₁₋₁₀ alkoxy" means an alkoxy group containing 1 to 10 carbon atoms, including, but not limited to, methoxy, ethoxy, propoxy, butoxy, etc.

Alkoxy may be optionally substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"Cycloalkyloxy" refers to -O-cycloalkyl, wherein the cycloalkyl is defined as above, for example, "C₃₋₁₀ cycloalkyloxy" means a cycloalkyloxy group containing 3 to 10 carbon atoms, including, but not limited to, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, etc.

Cycloalkyloxy may be optionally substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"Heterocyclyloxy" refers to -O-heterocyclyl, wherein heterocyclyl is defined as above, for example, "C₃₋₁₀ heterocyclyloxy" means a heterocyclyloxy group containing 3 to 10 carbon atoms, including, but not limited to, azacyclobutyloxy, oxacyclobutyloxy, azacyclopentyloxy, nitrogen, oxacyclohexyloxy, etc.

Heterocyclyloxy may be optionally substituted or unsubstituted, and when it is substituted, the substituent is preferably one or more of the groups independently selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈-S(O)_rR₁₂, -C₀₋₈-O-R₁₃, -C₀₋₈-C(O)OR₁₃, -C₀₋₈-C(O)R₁₃, -C₀₋₈-O-C(O)R₁₄, -C₀₋₈-NR₁₅R₁₆, -C₀₋₈-C(=NR₁₅)R₁₄, -C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈-C(O)NR₁₅R₁₆ and -C₀₋₈-N(R₁₅)-C(O)R₁₄.

"C₁₋₁₀ alkanoyl" refers to a monovalent atomic group which is obtained after a hydroxy group is removed from the C₁₋₁₀ alkyl acid, and is also generally referred to as

"C₀₋₉-C(O)-", for example, "C₁-C(O)-" refers to an acetyl; "C₂-C(O)-" refers to a propionyl; and "C₃-C(O)-" refers to a butyryl or isobutyryl.

"-C₀₋₈-S(O)_rR₁₂" means that the sulfur atom in -S(O)_rR₁₂ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

5 "-C₀₋₈-O-R₁₃" means that the oxygen atom in -O-R₁₃ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

"-C₀₋₈-C(O)OR₁₃" means that carbonyl in -C(O)OR₁₃ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

10 "-C₀₋₈-C(O)R₁₄" means that carbonyl in -C(O)R₁₄ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

"-C₀₋₈-O-C(O)R₁₄" means that the oxygen atom in -O-C(O)R₁₄ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

"-C₀₋₈-NR₁₅R₁₆" means that the nitrogen atom in -NR₁₅R₁₆ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

15 "-C₀₋₈-C(=NR₁₅)R₁₄" means that the nitrogen atom in -C(=NR₁₅)R₁₄ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

"-C₀₋₈-N(R₁₅)-C(=NR₁₆)R₁₄" means that the nitrogen atom in -N(R₁₅)-C(=NR₁₆)R₁₄ is attached to C₀₋₈ alkyl, wherein C₀ alkyl means a bond, and C₁₋₈ alkyl is defined as above.

20 "-C₀₋₈-C(O)NR₁₅R₁₆" means that carbonyl in -C(O)NR₁₅R₁₆ is attached to C₀₋₈ alkyl, wherein C₀ alkyl refers to a bond, and C₁₋₈ alkyl is defined as above.

"-C₀₋₈-N(R₁₅)-C(O)R₁₄" means that the nitrogen atom in -N(R₁₅)-C(O)R₁₄ is attached to C₀₋₈ alkyl, wherein C₀ alkyl means a bond, and C₁₋₈ alkyl is defined as above.

25 "C₁₋₁₀ haloalkyl" refers to an alkyl group having 1 to 10 carbon atoms in which hydrogens on the alkyl are optionally substituted by a fluorine, chlorine, bromine or iodine atom, including, but not limited to, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, tribromomethyl, etc.

30 "C₁₋₁₀ haloalkoxy" refers to an alkoxy group having 1 to 10 carbon atoms in which hydrogens on the alkyl are optionally substituted by a fluorine, chlorine, bromine or iodine atom, including, but not limited to, difluoromethoxy, dichloromethoxy, dibromomethoxy, trifluoromethoxy, trichloromethoxy, tribromomethoxy, etc.

"C₁₋₁₀ deuterioalkyl" refers to an alkyl group having 1 to 10 carbon atoms in which hydrogens on the alkyl are optionally substituted by a deuterium atom, including, but not limited to, monodeuteriomethyl, dideuteriomethyl, trideuteriomethyl, etc.

"Halogen" refers to fluorine, chlorine, bromine or iodine.

35 "DCM" refers to dichloromethane, "PE" refers to petroleum ether, "EtOAc"/"EA" refers to ethyl acetate, "MeOH" refers to methanol, "DMF" refers to *N,N*-dimethylformamide, "THF" refers to tetrahydrofuran, "DIPEA" refers to *N,N*-diisopropylethylamine, "DMP" refers to Dess-Martin Periodinane, with a chemical name as (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, "HATU" refers to 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, "LiAlH₄"

40

refers to lithium aluminum hydride, "NaBH₄" refers to sodium borohydride, "K₂CO₃" refers to potassium carbonate, "Na₂CO₃" refers to sodium carbonate, "NaHCO₃" refers to sodium bicarbonate, "NaOH" refers to sodium hydroxide, "KOAc" refers to potassium acetate, "K₃PO₄" refers to potassium phosphate, "HOAc" refers to acetic acid, "CaCl₂" refers to calcium chloride, "NBS" refers to N-bromosuccinimide, "PhI(OAc)₂" refers to iodobenzene diacetate, "Raney-Ni" refers to Raney nickel, "NaIO₄" refers to sodium periodate, "KMnO₄" refers to potassium permanganate, "NaBH₃CN" refers to sodium cyanoborohydride, "Pd(dppf)Cl₂" refers to [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride dichloromethane, and "S-Phos-Pd-G2" refers to chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II).

The term "optional" or "optionally" means that the event or circumstance subsequently described may, but not necessarily, occur, and that the description includes instances where the event or circumstance occurs or does not occur. For example, "heterocyclyl group optionally substituted by alkyl" means that alkyl may be, but not necessarily, present, and that the description includes instances where the heterocyclyl group is or is not substituted by alkyl.

The term "substituted" means that one or more hydrogen atoms in the group are each independently substituted by a corresponding number of substituents. It goes without saying that a substituent is only in its possible chemical position, and those skilled in the art will be able to determine (by experiments or theories) possible or impossible substitution without undue efforts. For example, it may be unstable when an amino or hydroxy having a free hydrogen is bound to a carbon atom having an unsaturated bond (such as olefin).

"Pharmaceutical composition" refers to a mixture containing one or more of the compounds described herein or a physiologically/pharmaceutically acceptable salt or pro-drug thereof, and other chemical components, for example physiologically/pharmaceutically acceptable carriers and excipients. The purpose of the pharmaceutical composition is to promote the administration to an organism, which facilitates the absorption of the active ingredient, thereby exerting biological activities.

The present invention is further explained in detail below with reference to examples, which are not intended to limit the present invention, and the present invention is not merely limited to the contents of the examples.

The compound structure of the present invention is determined by nuclear magnetic resonance (NMR) and/or liquid chromatography-mass spectrometry (LC-MS). The NMR chemical shift (δ) is given in parts per million (ppm). The NMR determination is conducted by using a Bruker AVANCE-400 or AVANCE-500 nuclear magnetic resonance apparatus, with hexadeuterodimethyl sulfoxide (DMSO-*d*₆), tetradeuteromethanol (CD₃OD), deuterium oxide (D₂O) and deuterated chloroform (CDCl₃) as determination solvents, and tetramethylsilane (TMS) as an internal standard.

The LC-MS determination is conducted by using an Agilent 6120 mass spectrometer. The HPLC determination is conducted by using an Agilent 1200 DAD high pressure liquid chromatograph (Sunfire C18 150 x 4.6 mm chromatographic column) and a Waters 2695-2996 high pressure liquid chromatograph (Gimini C18 150 x 4.6 mm chromatographic column).

Yantai Yellow Sea HSGF254 or Qingdao GF254 silica gel plate is adopted as a thin layer chromatography (TLC) silica gel plate. The specification adopted by TLC is 0.15-0.20 mm, and the specification adopted by thin layer chromatography for the separation of products is 0.4-0.5 mm. The Yantai Yellow Sea silica gel with 200 to 300 meshes is generally utilized as a carrier in column chromatography.

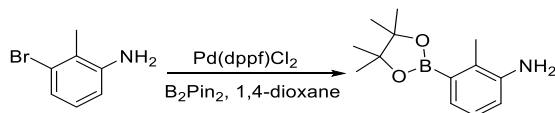
Starting materials in the examples of the present invention are known and commercially available, or may be synthesized by using or according to methods known in the art.

Unless otherwise stated, all reactions of the present invention are carried out under a dry nitrogen or argon atmosphere with continuous magnetic stirring, wherein the solvent is a dry solvent, and the reaction temperature is in degree centigrade (°C).

Preparation of Intermediates

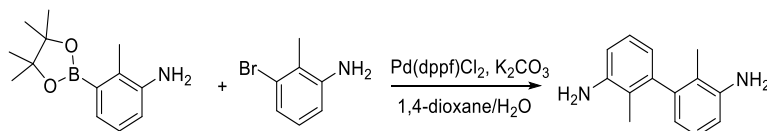
1. Preparation of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-formylpicolinamide)

Step 1: Synthesis of 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



3-bromo-2-methylaniline (2.0 g, 10.75 mmol) and *bis*(pinacolato)diboron (4.097 g, 16.13 mmol) were dissolved in 1,4-dioxane (30 mL), and then KOAc (3.161 g, 32.26 mmol) and Pd(dppf)Cl_2 (0.786 g, 1.08 mmol) were added. The nitrogen was charged to replace by evacuation for protection. The solution was heated to 80 °C and reacted for 16 hrs until the reaction was completed. The reaction solution was directly used in the next step without being further purified. MS m/z (ESI): 234 $[\text{M}+\text{H}]^+$.

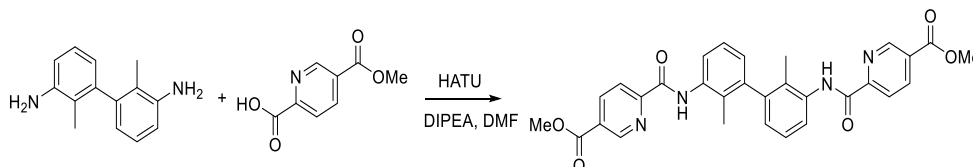
Step 2: Synthesis of 2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diamine



3-bromo-2-methylaniline (1.667 g, 8.96 mmol) was added to the above reaction solution, 1,4-dioxane (10 mL) and water (8 mL) were added. K_2CO_3 (3.71 g, 26.89 mmol) and Pd(dppf)Cl_2 (0.655 g, 0.90 mmol) were then added, and the nitrogen was charged to replace by evacuation for protection. The solution was heated to 95 °C and reacted for 2 hrs. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The obtained crude product was separated by rapid silica gel column

chromatography (PE/EA 2:1) to obtain 2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diamine (1.8 g, yield: 95%). MS m/z (ESI): 213 [M+H]⁺.

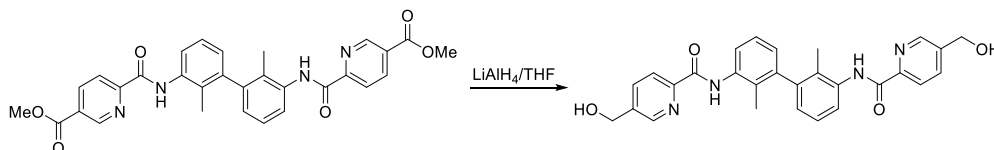
Step 3: Synthesis of dimethyl 6,6'-(((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))dinicotinate



2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diamine (2.0 g, 9.42 mmol) and 5-(methoxycarbonyl)picolinic acid (4.268 g, 23.55 mmol) were dissolved in DMF (20 mL), and DIPEA (6.076 g, 47.10 mmol) and HATU (10.74 g, 28.26 mmol) were then added.

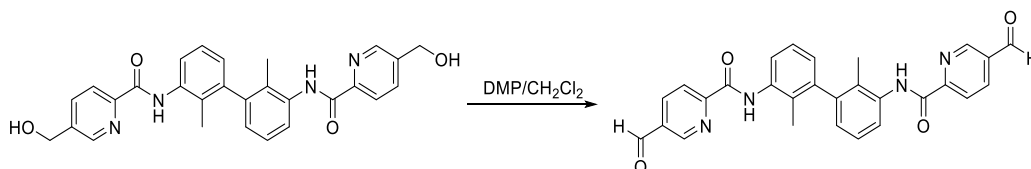
The reaction solution was stirred at room temperature for 0.5 hr. After the reaction was completed, the reaction mixture was filtered, and the filter cake was dried to obtain dimethyl 6,6'-(((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))dinicotinate (1.0 g, yield: 20%). MS m/z (ESI): 539 [M+H]⁺.

Step 4: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(hydroxymethyl)picolinamide)



Dimethyl 6,6'-(((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl)) dinicotinate (1.0 g, 1.86 mmol) was dissolved in tetrahydrofuran (20 mL), and LiAlH₄ (0.353 g, 9.28 mmol) was added in batches. After the addition, the reaction solution was stirred at room temperature for 2 hrs. After the reaction was completed, sodium sulfate decahydrate was added for quenching. The reaction solution was filtered, and the filtrate was concentrated. The crude product was separated by rapid silica gel column chromatography (PE/EA 1:1) to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(hydroxymethyl)picolinamide) (0.35 g, yield: 42%). MS m/z (ESI): 483 [M+H]⁺.

Step 5: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-formylpicolinamide)

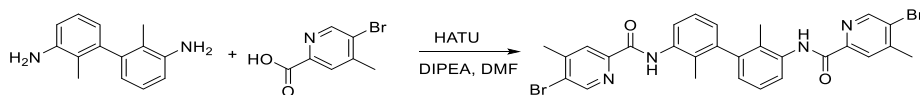


N,N'-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(hydroxymethyl)picolinamide) (350 mg, 0.73 mmol) was dissolved in dichloromethane (10 mL), and NaHCO₃ (366 mg, 4.35 mmol) and DMP (769 mg, 1.81 mmol) were then added. The reaction solution was stirred at room temperature for 1 hr. After the reaction was c

ompleted, the reaction solution was filtered, and the filtrate was concentrated. The crude product was separated by rapid silica gel column chromatography (PE/EA 1:1) to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-formylpicolinamide) (280 mg, yield: 81%). MS *m/z* (ESI): 479 [M+H]⁺.

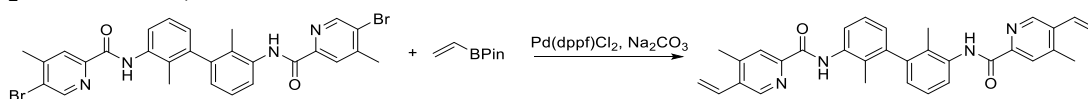
5 **2. Preparation of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-formyl-4-methoxypicolinamide)**

Step 1: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-bromo-4-methylpicolinamide)



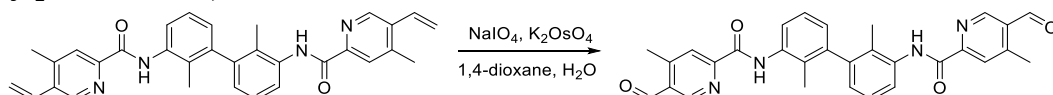
10 2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diamine (491 mg, 2.32 mmol) was dissolved in DMF (15 mL), 5-bromo-4-methylpicolinic acid (1000 mg, 4.63 mmol), DIPEA (1492 mg, 11.56 mmol) and HATU (2637 mg, 6.94 mmol) were then added, and the reaction solution was stirred at room temperature for 1 hr. The reaction solution was filtered, the filter cake was washed with ethyl acetate, and then dried to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-bromo-4-methylpicolinamide) (366 mg, yield: 26%). MS *m/z* (ESI): 609 [M+H]⁺.

Step 2: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-methyl-5-vinylpicolinamide)



20 *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-bromo-4-methylpicolinamide) (336 mg, 0.60 mmol) was dissolved in the mixture of 1,4-dioxane (10 mL) and water (2 mL), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (927 mg, 6.02 mmol), Na₂CO₃ (191 mg, 1.81 mmol) and Pd(dppf)Cl₂ (44 mg, 0.06 mmol) were then added, and the nitrogen was charged for protection. The solution was heated to 95 °C and reacted for 2 hrs. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The crude product was separated by silica gel column chromatography (PE/EA 2:1) to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-methyl-5-vinylpicolinamide) (260 mg, yield: 86%). MS *m/z* (ESI): 503 [M+H]⁺.

Step 3: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-formyl-4-methylpicolinamide)

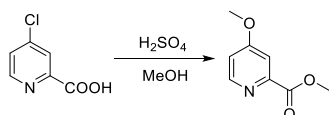


30 *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-methyl-5-vinylpicolinamide) (310 mg, 0.62 mmol) was dissolved in the mixture of 1,4-dioxane (10 mL) and water (3 mL), sodium periodate (396 mg, 1.85 mmol) and potassium osmate dihydrate (23 mg, 0.062 mmol) were then added, and the reaction solution was stirred at room temperature for 2 hrs. After the reaction was completed, the reaction solution was diluted with water,

and extracted three times with dichloromethane. The organic phases were combined, successively washed with water and a saturated brine, and dried over anhydrous sodium sulfate. The solution was filtrated and concentrated, and the crude product was separated by rapid silica gel column chromatography to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(5-formyl-4-methylpicolinamide) (46 mg, yield: 15%). MS *m/z* (ESI): 507 [M+H]⁺.

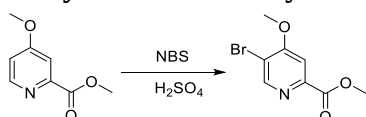
3. Preparation of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(5-formyl-4-methoxypicolinamide)

Step 1: Synthesis of methyl 4-methoxypicolinate



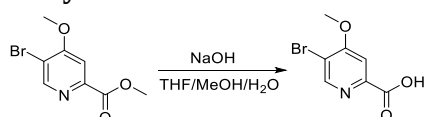
4-chloropicolinic acid (100 g, 0.64 mol) was added to methanol (500 mL), and concentrated sulfuric acid (4 mL) was then added, and the reaction solution was heated to 80 °C, and then stirred for 60 hrs. After the reaction was completed, the reaction solution was concentrated, added with a saturated sodium bicarbonate aqueous solution, and then extracted with ethyl acetate. The organic phase was successively washed with water and a saturated brine, and then dried over sodium sulfate. The obtained organic phase was filtered and concentrated. The crude product was separated by silica gel column chromatography [eluent: petroleum ether : ethyl acetate] to obtain methyl 4-methoxypicolinate (55.6 g, yield: 52%). MS *m/z* (ESI): 168 [M+H]⁺.

Step 2: Synthesis of methyl 5-bromo-4-methoxypicolinate



Methyl 4-methoxypicolinate (20 g, 0.12mol) was added to concentrated sulfuric acid (150 mL), NBS (38.3 g, 0.22 mol) was added, and the reaction solution was stirred at room temperature for 16 hrs. After the reaction was completed, water, a sodium bicarbonate aqueous solution were successively added and then extracted with ethyl acetate. The organic phases were combined, successively washed with water and a saturated brine, and then dried over anhydrous sodium sulfate. The obtained organic phase was filtered and concentrated. The crude product was separated by silica gel column chromatography to obtain methyl 5-bromo-4-methoxypicolinate (22.5 g, yield: 77%). MS *m/z* (ESI): 246/248 [M+H]⁺.

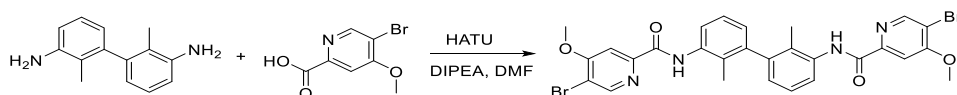
Step 3: Synthesis of 5-bromo-4-methoxypicolinic acid



Methyl 5-bromo-4-methoxypicolinate (22.5 g, 91.4 mmol) was dissolved in a mixture solvent of tetrahydrofuran (80 mL), methanol (80 mL) and water (32 mL), NaOH (9.1 g, 0.23 mol) was then added, and the reaction solution was stirred at room

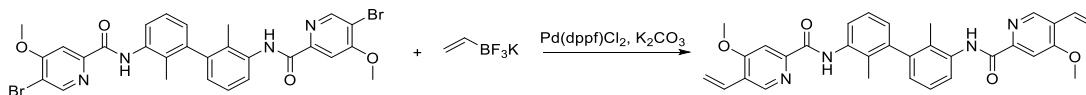
temperature for 0.5 hr. After the reaction was completed, the reaction solution was concentrated, neutralized with a 1N HCl solution, and then extracted with a mixture solvent of dichloromethane and methanol (12:1). The organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. The obtained organic phase was filtered, and concentrated to obtain 5-bromo-4-methoxypicolinic acid (19.1 g, yield: 90%). MS m/z (ESI): 232.2/234.2 [M+H]⁺.

Step 4: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-bromo-4-methoxypicolinamide)



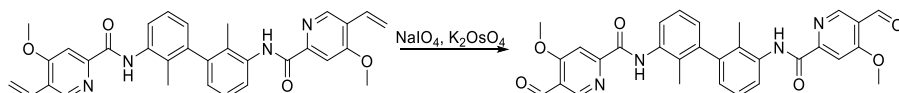
2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diamine (1.73 g, 8.2 mmol) and 5-bromo-4-methoxypicolinic acid (3.98 g, 17.2 mmol) were dissolved in DMF (30 mL), and *N,N*-diisopropylethylamine (5.27 g, 40.7 mmol) and 2-(azole benzotritinogen 7-oxide)-*N,N,N',N'*-tetramethylureahexafluorinephosphoric acid (9.30 g, 24.5 mmol) were then added, and the reaction solution was stirred at room temperature for 12 hrs. After the reaction was completed, the solid appeared in the solution was collected by filtering, and the filter cake was washed with ethyl acetate, and dried to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-bromo-4-methoxypicolinamide) (4.35 g, yield: 83%). MS m/z (ESI): 641.2 [M+H]⁺.

Step 5: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-methoxy-5-vinylpicolinamide)



N,N'-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-bromo-4-methoxypicolinamide) (4.35 g, 6.8 mmol) was added to the mixture of 1,4-dioxane (50 mL) and water (10 mL), and potassium carbonate (2.82 g, 20.4 mmol), potassium vinyltrifluoroborate (9.1 g, 68.0 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride (500 mg, 0.68 mmol) were successively added. Under a nitrogen atmosphere, the reaction solution was heated to 100 °C, and stirred for 5 hrs. After the reaction was completed, water and ethyl acetate was successively added to extract the reaction solution. The organic phases were combined, successively washed with water and a saturated brine, and then dried over anhydrous sodium sulfate. The obtained organic phase was filtered and concentrated. The crude product was separated by silica gel column chromatography [eluent: dichloromethane : methanol] to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-methoxy-5-vinylpicolinamide) (3.63 g, yield: 100%). MS m/z (ESI): 535.4 [M+H]⁺.

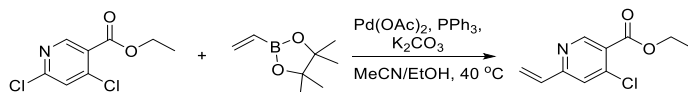
Step 6: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-formyl-4-methoxypicolinamide)



N,N'-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(4-methoxy-5-vinylpicolinamide) (3.63 g, 6.8 mmol) was added to a mixture of 1,4-dioxane (60 mL) and water (18 mL), and then sodium periodate (8.71 g, 40.7 mmol) and potassium osmate dihydrate (500 mg, 1.36 mmol) were successively added, and the reaction solution was stirred at room temperature for 0.5 hr. After the reaction was completed, water and dichloromethane were added to extract the reaction solution, and the organic phases were combined and then dried over anhydrous sodium sulfate. The obtained organic phase was filtered and concentrated. The crude product was separated by silica gel column chromatography [eluent: petroleum ether : ethyl acetate] to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(5-formyl-4-methoxypicolinamide) (1.51 g, yield: 41%). MS *m/z* (ESI): 539.2 [M+H]⁺.

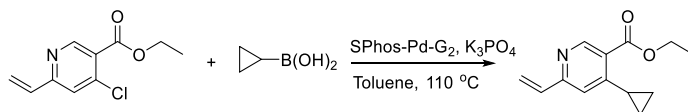
4. Preparation of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(4-cyclopropyl-5-formylpicolinamide)

Step 1: Synthesis of ethyl 4-chloro-6-vinylnicotinate



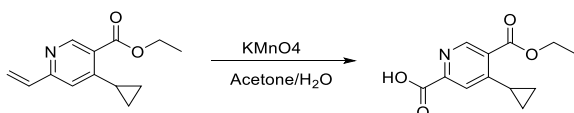
Ethyl 4,6-dichloronicotinate (10 g, 45.45 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (7.7 g, 50 mmol), palladium acetate (0.51 g, 2.27 mmol), triphenylphosphine (1.19 g, 4.55 mmol) and potassium carbonate (12.54 g, 90.9 mmol) were dissolved in a mixed solvent of acetonitrile and ethanol (300 mL, 2:1). The nitrogen was charged to replace by evacuation for protection. The reaction solution was heated to 40 °C, and then stirred overnight. After the reaction was completed, the reaction solution was filtered, the filter cake was washed with ethyl acetate, and the filtrate was concentrated. The crude product was separated by silica gel column chromatography (PE/EA = 10/1) to obtain ethyl 4-chloro-6-vinylnicotinate (8.64 g, yield: 90%). MS *m/z* (ESI): 212 [M+H]⁺.

Step 2: Synthesis of ethyl 4-cyclopropyl-6-vinylnicotinate



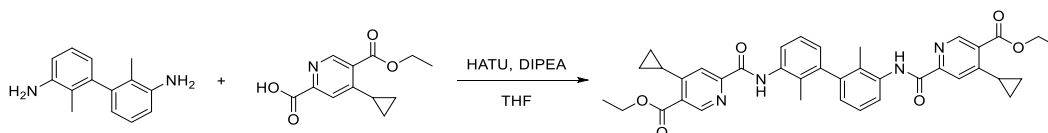
Ethyl 4-chloro-6-vinylnicotinate (5.0 g, 23.7 mmol), cyclopropylboronic acid (6.1 g, 71.1 mmol), SPhos-Pd-G2 (0.85 g, 1.185 mmol) and K₃PO₄ (10 g, 47.4 mmol) were dissolved in toluene (100 mL), and the nitrogen was charged to replace by evacuation for protection. The reaction solution was heated to 110 °C, and then stirred overnight. After the reaction was completed, the reaction solution was concentrated. The crude product was separated by silica gel column chromatography (PE/EA = 10/1) to obtain ethyl 4-cyclopropyl-6-vinylnicotinate (2.5 g, yield: 48%). MS *m/z* (ESI): 218 [M+H]⁺.

Step 3: Synthesis of 4-cyclopropyl-5-(ethoxycarbonyl)picolinic acid



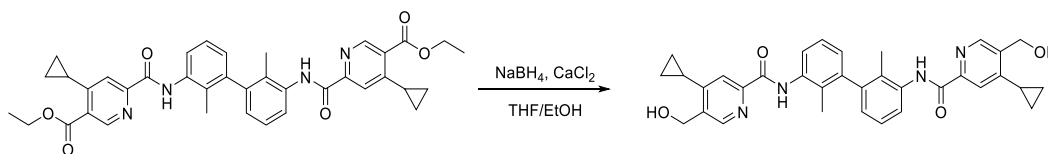
Ethyl 4-cyclopropyl-6-vinylnicotinate (2.5 g, 11.52 mmol) was dissolved in a mixture solvent of acetone and water (60 mL/30 mL), KMnO_4 (5.46 g, 34.56 mmol) was added, the reaction solution was stirred at room temperature for 48 hrs, and LCMS monitored whether the reaction was completed. The reaction solution was filtered, and the filtrate cake was washed with an appropriate amount of acetone. The filtrate was concentrated, and separated by silica gel column chromatography to obtain 4-cyclopropyl-5-(ethoxycarbonyl)picolinic acid (1.86 g, yield: 69%). MS m/z (ESI): 256 $[\text{M}+\text{H}]^+$.

Step 4: Synthesis of diethyl 6,6'-(((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylnicotinate)



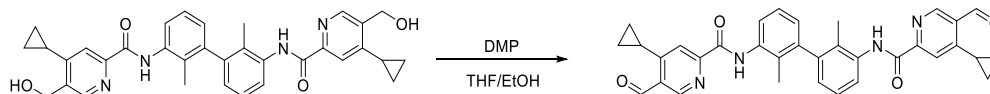
4-cyclopropyl-5-(ethoxycarbonyl)picolinic acid (1.86 g, 7.91 mmol) and 2,2'-dimethyl-1,1'-biphenyl-3,3'-diamine (0.84 g, 3.96 mmol) were dissolved in THF (150 mL), HATU (4.51 g, 11.87 mmol) and DIPEA (1.53 g, 11.87 mmol) were added after the mixture was substantially mixed, and the reaction solution was stirred overnight at room temperature. After the reaction was completed, silica gel was directly mixed with the sample, and the mixture was separated by silica gel column chromatography (PE/EA = 5/1) to obtain diethyl 6,6'-(((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylnicotinate) (2.1 g, yield: 75%). MS m/z (ESI): 324 $[1/2\text{M}+\text{H}]^+$; 647 $[\text{M}+\text{H}]^+$.

Step 5: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-cyclopropyl-5-(hydroxymethyl)picolinamide)



Diethyl 6,6'-(((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylnicotinate) (1.0 g, 1.55 mmol) was dissolved in a mixture solvent of ethanol and tetrahydrofuran (25 mL/50 mL), and then anhydrous CaCl_2 (1.0 g, 9.30 mmol) was added. The solution was stirred for 5 min, and NaBH_4 (0.35 g, 9.30 mmol) was then added. The solution was stirred at room temperature for 4 to 6 hrs until the reaction was completed. HOAc was added for quenching, the reaction solution was stirred for 0.5 hr, filtered, and washed with tetrahydrofuran. The filtrate was concentrated to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-cyclopropyl-5-(hydroxymethyl)picolinamide) (1.2 g), which was directly used in the next step. MS m/z (ESI): 282 $[1/2\text{M}+\text{H}]^+$; 563 $[(\text{M}+\text{H})]^+$.

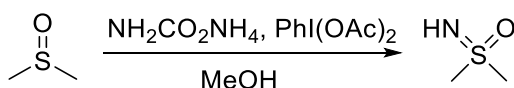
Step 6: Synthesis of *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-cyclopropyl-5-formylpicolinamide)



N,N'-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-cyclopropyl-5-(hydroxymethyl)picolinamide) (1.2 g, 1.55 mmol) was dissolved in a mixture of dichloromethane and tetrahydrofuran, and then Dess-Martin Periodinane (1.97 g, 4.65 mmol) was added. The solution was stirred at room temperature for 2 hrs, added with a saturated sodium bicarbonate aqueous solution (100 mL), and then extracted with dichloromethane, and the organic phase was dried over sodium sulfate. The obtained organic phase was filtrated, concentrated, and separated by silica gel column chromatography (5% MeOH/DCM) to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-cyclopropyl-5-formylpicolinamide) (1.1 g, yield in two steps: quantitative yield). MS *m/z* (ESI): 280 [1/2M+H]⁺; 559 [M+H]⁺.

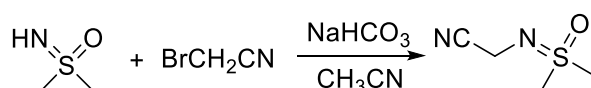
5. Preparation of ((2-aminoethyl)imino)dimethyl- λ^6 -sulfanone

Step 1: Synthesis of iminodimethyl- λ^6 -sulfanone



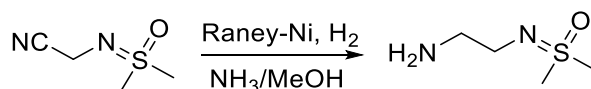
Dimethyl sulfoxide (1.0 g, 12.8 mmol) was added to methanol (50 mL), and PhI(OAc)₂ (12.4 g, 38.4 mmol) and ammonium carbamate (4.0 g, 51.2 mmol) were then added. The reaction solution was stirred at room temperature for 1 hr. After the reaction was completed, the reaction solution was concentrated, and separated by silica gel column chromatography (eluent: dichloromethane/methanol) to obtain iminodimethyl- λ^6 -sulfanone (1.01 g, yield: 85%).

Step 2: Synthesis of 2-((dimethyl(oxo)- λ^6 -sulfaneylidene)amino)acetonitrile



Iminodimethyl- λ^6 -sulfanone (374 mg, 4.02 mmol) was dissolved in acetonitrile (15 mL), bromoacetonitrile (576 mg, 4.82 mmol) and NaHCO₃ (506 mg, 6.0 mmol) were then added, and the solution was heated to 88 °C and then reacted for 16 hrs. After the reaction was completed, the reaction solution was filtered, and the filtrate was concentrated, and separated by silica gel column chromatography (eluent: dichloromethane/methanol) to obtain 2-((dimethyl(oxo)- λ^6 -sulfaneylidene)amino)acetonitrile (212 mg, yield: 40%). MS *m/z* (ESI): 133 [M+H]⁺; 265 [2M+H]⁺.

Step 3: Synthesis of ((2-aminoethyl)imino)dimethyl- λ^6 -sulfanone

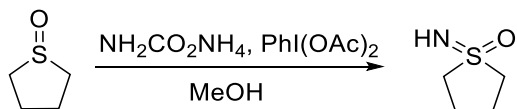


2-((dimethyl(oxo)- λ^6 -sulfaneylidene)amino)acetonitrile (257 mg, 1.94 mmol) was dissolved in 2 M solution of ammonia in methanol (15 mL), Raney-Ni (20 mg) was added,

and the reaction solution was stirred at room temperature for 16 hrs under a hydrogen atmosphere. After the reaction was completed, the reaction solution was filtered, and the filtrate was concentrated to obtain ((2-aminoethyl)imino)dimethyl- λ^6 -sulfanone (267 mg, yield: 100%). MS m/z (ESI): 137.2 [M+H]⁺.

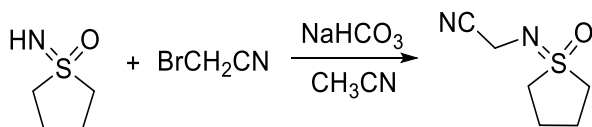
5 **6. Preparation of 1-((2-aminoethyl)imino)tetrahydro-1*H*-1 λ^6 -thiophene 1-oxide**

Step 1: Synthesis of 1-iminotetrahydro-1*H*-1 λ^6 -thiophene 1-oxide



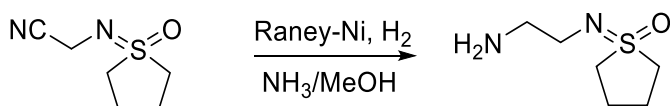
Tetrahydrothiophene 1-oxide (500 mg, 4.8 mmol) was added to methanol (20 mL), and then PhI(OAc)₂ (4.64 g, 14.4 mmol) and ammonium carbamate (1.5 g, 19.2 mmol) were added, and the reaction solution was stirred at room temperature for 1 hr. After the reaction was completed, the reaction solution was concentrated, and separated by silica gel column chromatography (eluent: dichloromethane/methanol) to obtain 1-iminotetrahydro-1*H*-1 λ^6 -thiophene 1-oxide (385 mg, yield: 67%). MS m/z (ESI): 102.2 [M+H]⁺.

15 **Step 2: Synthesis of 2-((1-oxidotetrahydro-1 λ^6 -thiophen-1-ylidene)amino)acetonitrile**



1-iminotetrahydro-1*H*-1 λ^6 -thiophene 1-oxide (385 mg, 3.23 mmol) was dissolved in acetonitrile (15 mL), and then bromoacetonitrile (463 mg, 3.87 mmol) and NaHCO₃ (407 mg, 4.84 mmol) were added, and the reaction solution was heated to 88 °C and stirred for 16 hrs. After the reaction was completed, the reaction solution was filtered, and the filtrate was concentrated, and separated by silica gel column chromatography (eluent: dichloromethane/methanol) to obtain 2-((1-oxidotetrahydro-1 λ^6 -thiophen-1-ylidene)amino)acetonitrile (281 mg, yield: 55%). MS m/z (ESI): 159 [M+H]⁺.

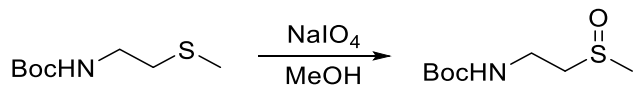
Step 3: Synthesis of 1-((2-aminoethyl)imino)tetrahydro-1*H*-1 λ^6 -thiophene 1-oxide



2-((1-oxidotetrahydro-1 λ^6 -thiophen-1-ylidene)amino)acetonitrile (281 mg, 1.78 mmol) was dissolved in 2 M solution of ammonia in methanol (15 mL), and then Raney-Ni (20 mg) was added, and the reaction solution was stirred at room temperature for 16 hrs under a hydrogen atmosphere. After the reaction was completed, the reaction solution was filtered, and the filtrate was concentrated to obtain 1-((2-aminoethyl)imino)tetrahydro-1*H*-1 λ^6 -thiophene 1-oxide (248 mg, yield: 86%). MS m/z (ESI): 163.2 [M+H]⁺.

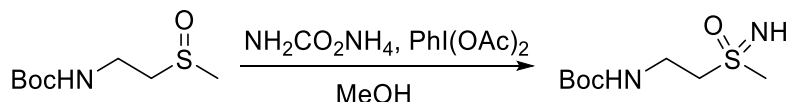
7. Preparation of (2-aminoethyl)(imino)(methyl)- λ^6 -sulfanone

Step 1: Synthesis of *tert*-butyl (2-(methylsulfinyl)ethyl)carbamate



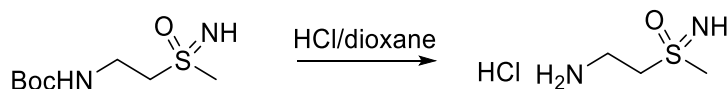
Tert-butyl (2-(methylthio)ethyl)carbamate (1.0 g, 5.23 mmol) was dissolved in a mixture of methanol (20 mL) and water (20 mL), and NaIO₄ (1.12 g, 5.23 mmol) was added under an ice bath. The reaction solution was stirred at room temperature for 16 hrs. After the reaction was completed, water and ethyl acetate were added to extract the reaction solution. The organic phases were combined, successively washed with water and a saturated brine, and then dried over anhydrous sodium sulfate. The obtained organic phase was filtered, concentrated, and separated by silica gel column chromatography (eluent: petroleum ether/ethyl acetate) to obtain *tert*-butyl (2-(methylsulfinyl)ethyl)carbamate (1.06 g, yield: 98%). MS *m/z* (ESI): 208.2 [M+H]⁺.

Step 2: Synthesis of *tert*-butyl (2-(*S*-methylsulfonimidoyl)ethyl)carbamate



Tert-butyl (2-(methylsulfinyl)ethyl)carbamate (1.06 g, 5.11 mmol) was dissolved in methanol (25 mL), PhI(OAc)₂ (4.94 g, 15.3 mmol) and ammonium carbamate (1.6 g, 20.45 mmol) were then added, and the reaction solution was stirred at room temperature for 1 hr. After the reaction was completed, the reaction solution was concentrated, and separated by silica gel column chromatography (eluent: dichloromethane/methanol) to obtain *tert*-butyl (2-(*S*-methylsulfonimidoyl)ethyl)carbamate (827 mg, yield: 73%). MS *m/z* (ESI): 223.2 [M+H]⁺.

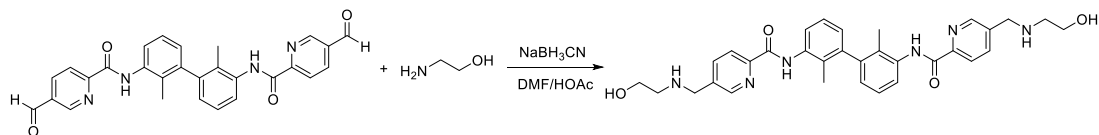
Step 3: Synthesis of (2-aminoethyl)(imino)(methyl)- λ^6 -sulfanone



Tert-butyl (2-(*S*-methylsulfonimidoyl)ethyl)carbamate (370 mg, 1.66 mmol) was dissolved in a 4 M solution of hydrochloric acid in 1,4-dioxane (10 mL), and the reaction solution was stirred at room temperature for 1 hr. After the reaction was completed, the reaction solution was filtered, and the filtrate was concentrated to obtain (2-aminoethyl)(imino)(methyl)- λ^6 -sulfanone (325 mg, yield: 100%). MS *m/z* (ESI): 105.2 [M-NH₂]⁺.

Preparation of Specific Examples

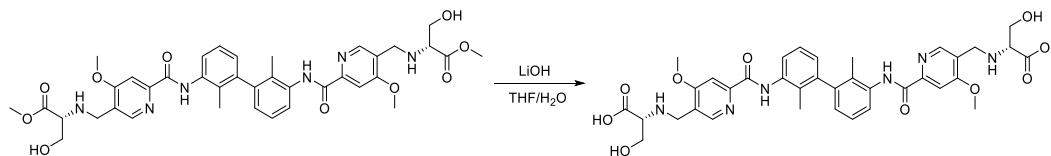
Example 1: Preparation of N,N'-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((2-hydroxyethyl)amino)methyl)picolinamide)



N,N'-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(5-formylpicolinamide) (50 mg, 0.104 mmol) was dissolved in DMF (3 mL), and then 2-aminoethan-1-ol (64 mg, 1.045 mmol) and acetic acid (0.5 mL) were added, and the reaction solution was stirred at room temperature for 2 hrs. NaBH₃CN (66 mg, 1.045 mmol) was then added, and the reaction solution was stirred overnight at room temperature. After the reaction was completed, the reaction solution was separated by reversed-phase column chromatography to obtain *N,N'*-(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(5-(((2-hydroxyethyl)amino)methyl)picolinamide) (7.7 mg, yield: 13%). MS *m/z* (ESI): 569 [M+H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 (s, 2H), 8.74 (d, *J* = 2.0 Hz, 2H), 8.26 – 8.03 (m, 4H), 7.85 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.00 (dd, *J* = 7.5, 1.3 Hz, 2H), 4.05 (s, 4H), 3.56 (t, *J* = 5.5 Hz, 4H), 2.76 (t, *J* = 5.6 Hz, 4H), 2.02 (s, 6H).

Example 2: Preparation of (2*R*,2'*R*)-2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(azanediyl))*bis*(carbonyl))*bis*(4-methoxypyridine-6,3-diyl))*bis*(methylene))*bis*(azanediyl))*bis*(3-hydroxypropanoic acid)



Dimethyl 2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(azanediyl))*bis*(carbonyl))*bis*(4-methoxypyridine-6,3-diyl))*bis*(methylene))*bis*(azanediyl))(2*R*,2'*R*)-*bis*(3-hydroxypropanoate) (54 mg, 0.073 mmol) was dissolved in tetrahydrofuran (1.6 mL) and water (0.4 mL), and then lithium hydroxide (24 mg, 0.58 mmol) was added, and the reaction solution was stirred at room temperature for 1 hr. After the reaction was completed, the reaction solution was concentrated and then acidized with 1N HCl to achieve a pH of 2-3. The solution was directly separated by reverse-phase column chromatography to obtain (2*R*,2'*R*)-2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)*bis*(azanediyl))*bis*(carbonyl))*bis*(4-methoxypyridine-6,3-diyl))*bis*(methylene))*bis*(azanediyl))*bis*(3-hydroxypropanoic acid) (28.7 mg, yield: 56%). MS *m/z* (ESI): 717.6 [M+H]⁺; 359.4 [1/2M+H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.38 (s, 2H), 8.54 (s, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.74 (s, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 7.4 Hz, 2H), 3.99 (s, 6H), 3.97 – 3.76 (m, 4H), 3.58 (m, 4H), 3.06 (t, *J* = 5.5 Hz, 2H), 2.01 (s, 6H).

The preparation of the compounds of examples 3 to 141 can be obtained by referring to the synthesis method of example 1 or 2:

Example No.	Structure	Name	MS: <i>m/z</i> [M+1] ⁺
3		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((2-hydroxyethyl)amino)methyl)-4-methoxypicolinamide)	629

4		dimethyl 2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2 <i>R</i> ,2' <i>R</i>)-bis(3-hydroxypropanoate)	745
5		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((2-hydroxyethyl)amino)methyl)-4-methylpicolinamide)	597
6		(2 <i>R</i> ,2' <i>R</i>)-2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(pyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(3-hydroxypropanoic acid)	657
7		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((2-methoxyethyl)amino)methyl)-4-methylpicolinamide)	625
8		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((1,3-dihydroxypropan-2-yl)amino)methyl)-4-methylpicolinamide)	657
9		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-methyl-5-(morpholinomethyl)picolinamide)	649
10		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((1-hydroxycyclopropyl)amino)methyl)-4-methylpicolinamide)	649
11		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-((3-hydroxy-3-methylazetidin-1-yl)methyl)-4-methylpicolinamide)	649
12		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-methyl-5-(pyrrolidin-1-ylmethyl)picolinamide)	617

13		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((<i>R</i>)-3-hydroxypyrrolidin-1-yl)methyl)-4-methylpicolinamide)	649
14		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((3,3-difluoropyrrolidin-1-yl)methyl)-4-methylpicolinamide)	689
15		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((cyclopropylamino)methyl)-4-methylpicolinamide)	589
16		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((2-acetamidoethyl)amino)methyl)-4-methylpicolinamide)	679
17		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methyl-5-(((3-oxopiperazin-1-yl)methyl)methyl)picolinamide)	675
18		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((3 <i>S</i> ,4 <i>R</i>)-3-hydroxytetrahydro-2 <i>H</i> -pyran-4-yl)amino)methyl)-4-methylpicolinamide)	709
19		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((1 <i>r</i> ,4 <i>r</i>)-4-hydroxycyclohexyl)amino)methyl)-4-methylpicolinamide)	705
20		dimethyl 2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azane diyl))(2 <i>R</i> ,2' <i>R</i>)- <i>bis</i> (3-hydroxypropanoate)	713
21		(2 <i>R</i> ,2' <i>R</i>)-2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azane diyl)) <i>bis</i> (3-hydroxypropanoic acid)	685

22		dimethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2S,2'S)-bis(3-hydroxypropanoate)	713
23		(2S,2'S)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(3-hydroxypropanoic acid)	685
24		dimethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))diacetate	653
25		2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))diacetic acid	625
26		dimethyl 1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))(2S,2'S)-bis(piperidine-2-carboxylate)	761
27		(2S,2'S)-1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))bis(piperidine-2-carboxylic acid)	733
28		dimethyl 1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))(2R,2'R)-bis(piperidine-2-carboxylate)	761

29		(2 <i>R</i> ,2' <i>R</i>)-1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))bis(piperidine-2-carboxylic acid)	733
30		(2 <i>R</i> ,2' <i>R</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methylpyridine-6,3-diyl))bis(methylene))bis(azanediyl))bis(4-hydroxybutanoic acid)	713
31		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(4-methoxy-5-(morpholinomethyl)picolinamide)	681
32		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(4-methoxy-5-((methylamino)methyl)picolinamide)	569
33		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(5-(((<i>S</i>)-2,3-dihydroxypropyl)amino)methyl)-4-methoxypicolinamide)	689
34		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(4-methoxy-5-(((2-methoxyethyl)amino)methyl)picolinamide)	657
35		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(5-(((2-(difluoromethoxy)ethyl)amino)methyl)-4-methoxypicolinamide)	729
36		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(4-methoxy-5-(((2-methoxyethyl)(methyl)amino)methyl)picolinamide)	685
37		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(5-(((2-hydroxyethyl)(methyl)amino)methyl)-4-methoxypicolinamide)	657

38		((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(ethane-2,1-diyl) diacetate	713
39		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((2-acetamidoethyl)amino)methyl)-4-methoxypicolinamide)	711
40		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((2-hydroxy-2-methylpropyl)amino)methyl)-4-methoxypicolinamide)	685
41		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-((((1-hydroxycyclopropyl)methyl)amino)methyl)-4-methoxypicolinamide)	681
42		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-((((<i>R</i>)-1-hydroxypropan-2-yl)amino)methyl)-4-methoxypicolinamide)	657
43		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-((((<i>S</i>)-1-hydroxypropan-2-yl)amino)methyl)-4-methoxypicolinamide)	657
44		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-((((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclopentyl)amino)methyl)-4-methoxypicolinamide)	709
45		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((3-hydroxyazetidin-1-yl)methyl)-4-methoxypicolinamide)	653
46		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-(((3-hydroxy-3-methylazetidin-1-yl)methyl)-4-methoxypicolinamide)	681
47		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(5-((((<i>R</i>)-3-hydroxypyrrolidin-1-yl)methyl)-4-methoxypicolinamide)	681

		yl)methyl)-4-methoxypicolinamide)	
48		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((<i>S</i>)-3-hydroxypyrrolidin-1-yl)methyl)-4-methoxypicolinamide)	681
49		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-((4-hydroxypiperidin-1-yl)methyl)-4-methoxypicolinamide)	709
50		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((<i>R</i>)-3-methoxypyrrolidin-1-yl)methyl)picolinamide)	709
51		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-((3-methoxyazetidin-1-yl)methyl)picolinamide)	681
52		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-((3-methoxy-3-methylazetidin-1-yl)methyl)picolinamide)	709
53		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((1 <i>s</i> ,3 <i>s</i>)-3-hydroxycyclobutyl)amino)methyl)-4-methoxypicolinamide)	681
54		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-((oxetan-3-ylamino)methyl)picolinamide)	653
55		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((<i>S</i>)-tetrahydrofuran-3-yl)amino)methyl)picolinamide)	681
56		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((<i>R</i>)-tetrahydrofuran-3-yl)amino)methyl)picolinamide)	681
57		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-((1-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-4-methoxypicolinamide)	705

		yl)methyl)-4-methoxypicolinamide)	
58		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-4-methoxypicolinamide)	705
59		(3 <i>S</i> ,3' <i>S</i>)-4,4'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azanediy)) <i>bis</i> (3-hydroxybutanoic acid)	745
60		(1 <i>s</i> ,1' <i>s</i> ,3 <i>s</i> ,3' <i>s</i>)-3,3'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azanediy)) <i>bis</i> (cyclobutane-1-carboxylic acid)	737
61		(2' <i>S</i>)-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>di</i> -L-proline	737
62		(2 <i>S</i> ,2' <i>S</i> ,4 <i>R</i> ,4' <i>R</i>)-1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (4-hydroxypyrrolidine-2-carboxylic acid)	769
63		(3 <i>S</i> ,3' <i>S</i>)-4,4'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (morpholine-3-carboxylic acid)	769
64		dimethyl 1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene))(2 <i>S</i> ,2' <i>S</i>)- <i>bis</i> (piperidine-2-carboxylate)	793

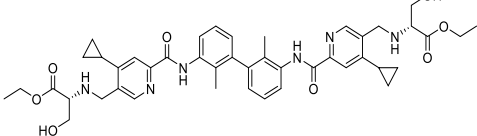
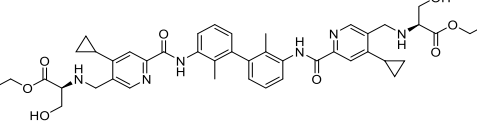
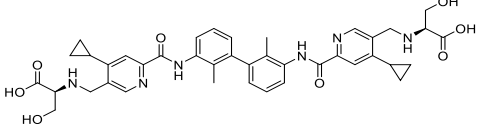
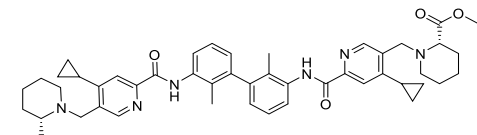
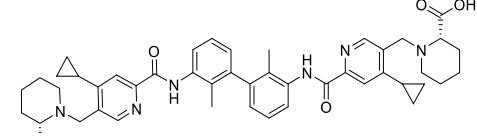
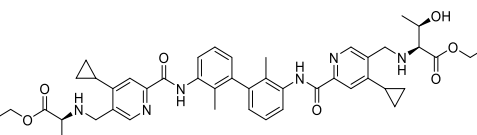
65		(2 <i>S</i> ,2' <i>S</i>)-1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (piperidine-2-carboxylic acid)	765
66		dimethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azane diyl))diacetate	685
67		2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azane diyl))diacetic acid	657
68		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((<i>S</i>)-2-oxotetrahydrofuran-3-yl)amino)methyl)picolinamide)	709
69		(2 <i>S</i> ,2' <i>S</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azane diyl)) <i>bis</i> (4-hydroxybutanoic acid)	745
70		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((<i>R</i>)-2-oxotetrahydrofuran-3-yl)amino)methyl)picolinamide)	709
71		(2 <i>R</i> ,2' <i>R</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azane diyl)) <i>bis</i> (4-hydroxybutanoic acid)	745
72		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((<i>S</i>)-5-oxotetrahydrofuran-3-yl)amino)methyl)picolinamide)	709

73		(3 <i>S</i> ,3' <i>S</i>)-3,3'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(4-hydroxybutanoic acid)	745
74		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(4-methoxy-5-(((<i>R</i>)-5-oxotetrahydrofuran-3-yl)amino)methyl)picolinamide)	709
75		(3 <i>R</i> ,3' <i>R</i>)-3,3'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(4-hydroxybutanoic acid)	745
76		dimethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))((2 <i>R</i> ,2' <i>R</i>))-bis(3-methoxypropanoate)	773
77		(2 <i>R</i> ,2' <i>R</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(3-methoxypropanoic acid)	745
78		dimethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))((2 <i>S</i> ,2' <i>S</i>))-bis(3-methoxypropanoate)	773
79		(2 <i>S</i> ,2' <i>S</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-methoxypyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(3-methoxypropanoic acid)	745

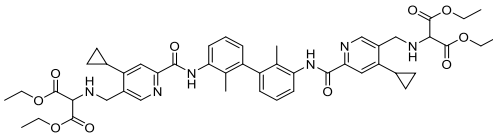
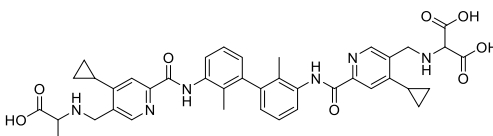
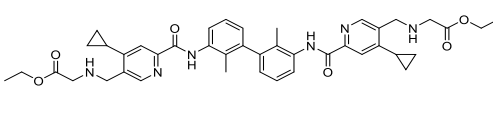
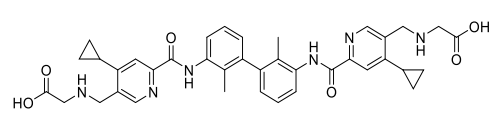
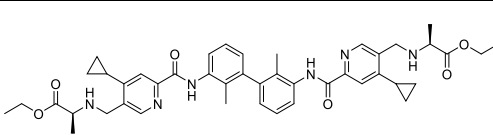
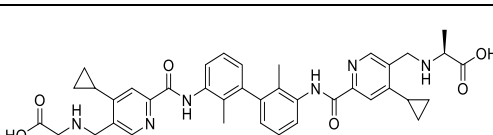
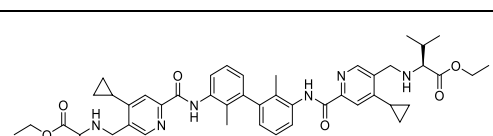
80		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((2-(methylsulfonyl)ethyl)amino)methyl)picolinamide)	753
81		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((2-(methylsulfinyl)ethyl)amino)methyl)picolinamide)	721
82		dimethyl 1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene))(3 <i>S</i> ,3' <i>S</i>)- <i>bis</i> (pyrrolidine-3-carboxylate)	765
83		(3 <i>S</i> ,3' <i>S</i>)-1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (pyrrolidine-3-carboxylic acid)	737
84		dimethyl 1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (piperidine-4-carboxylate)	793
85		1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-methoxypyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (piperidine-4-carboxylic acid)	765
86		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((<i>R</i>)-1-amino-3-hydroxy-1-oxopropan-2-yl)amino)methyl)-4-methoxypicolinamide)	715
87		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((<i>R</i>)-1-(ethylamino)-3-hydroxy-1-oxopropan-2-yl)amino)methyl)-4-methoxypicolinamide)	771

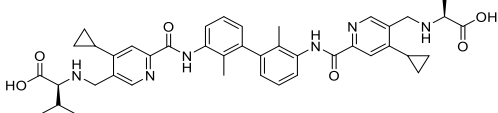
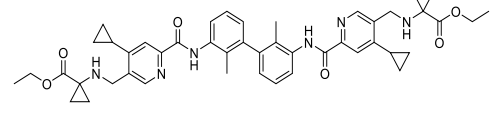
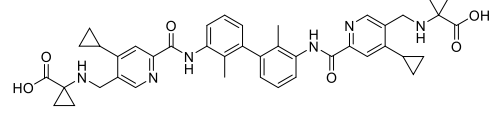
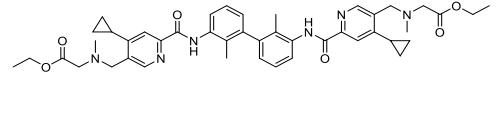
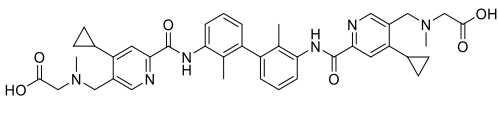
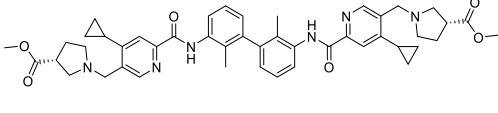
88		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((2-(<i>S</i> -methylsulfonimidoyl)ethyl)amino)methyl)picolinamide)	751
89		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((2-((dimethyl(oxo)-λ ⁶ -sulfaneylidene)amino)ethyl)amino)methyl)-4-methoxypicolinamide)	779
90		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-methoxy-5-(((2-((1-oxidotetrahydro-1λ ⁶ -thiophen-1-ylidene)amino)ethyl)amino)methyl)picolinamide)	831
91		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((2-hydroxyethyl)amino)methyl)picolinamide)	649
92		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((1,3-dihydroxypropan-2-yl)amino)methyl)picolinamide)	709
93		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((2-acetamidoethyl)amino)methyl)-4-cyclopropylpicolinamide)	731
94		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((1-hydroxycyclopropyl)methyl)amino)methyl)picolinamide)	701
95		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((<i>R</i>)-1-hydroxypropan-2-yl)amino)methyl)picolinamide)	677
96		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((<i>S</i>)-1-hydroxypropan-2-yl)amino)methyl)picolinamide)	677

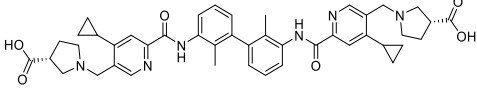
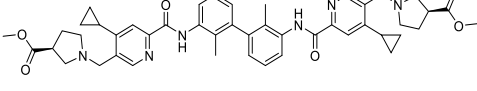
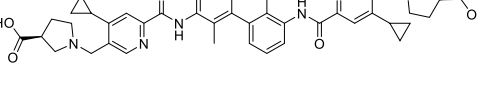
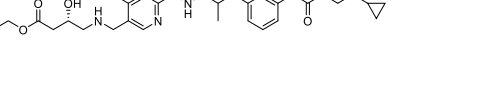
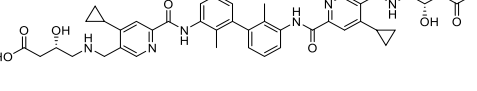
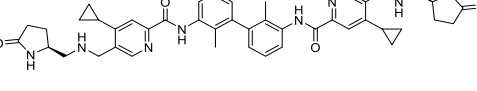
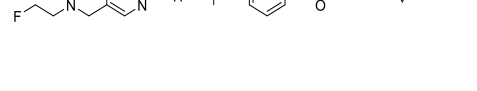
97		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclopentyl)amino)methyl)picolinamide)	729
98		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-((3-hydroxyazetidin-1-yl)methyl)picolinamide)	673
99		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-((3-hydroxy-3-methylazetidin-1-yl)methyl)picolinamide)	701
100		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((<i>R</i>)-3-hydroxypyrrolidin-1-yl)methyl)picolinamide)	701
101		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((<i>S</i>)-3-hydroxypyrrolidin-1-yl)methyl)picolinamide)	701
102		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-((4-hydroxypiperidin-1-yl)methyl)picolinamide)	729
103		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((1 <i>S</i> ,3 <i>S</i>)-3-hydroxycyclobutyl)amino)methyl)picolinamide)	701
104		dimethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-cyclopropylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azanediyl))(2 <i>R</i> ,2' <i>R</i>)- <i>bis</i> (3-hydroxypropanoate)	765
105		(2 <i>R</i> ,2' <i>R</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-cyclopropylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azanediyl)	737

		yl))bis(3-hydroxypropanoic acid)	
106		diethyl 2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2R,2'R)-bis(3-hydroxypropanoate)	793
107		diethyl 2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2S,2'S)-bis(3-hydroxypropanoate)	793
108		(2S,2'S)-2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azanediyl))bis(3-hydroxypropanoic acid)	737
109		dimethyl 1,1'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))(2S,2'S)-bis(piperidine-2-carboxylate)	813
110		(2S,2'S)-1,1'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(piperidine-2-carboxylic acid)	785
111		diethyl 2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2S,2'S,3R,3'R)-bis(3-hydroxybutanoate)	821

112		(2 <i>S</i> ,2' <i>S</i> ,3 <i>R</i> ,3' <i>R</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(3-hydroxybutanoic acid)	765
113		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(4-cyclopropyl-5-(((<i>S</i>)-2-oxotetrahydrofuran-3-yl)amino)methyl)picolinamide)	729
114		(2 <i>S</i> ,2' <i>S</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(4-hydroxybutanoic acid)	765
115		tetraethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2 <i>S</i> ,2' <i>S</i>)-disuccinate	905
116		(2 <i>S</i> ,2' <i>S</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))disuccinic acid	793
117		tetraethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2 <i>R</i> ,2' <i>R</i>)-disuccinate	905
118		(2 <i>R</i> ,2' <i>R</i>)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(4-hydroxybutanoic acid)	793

		diyl))disuccinic acid	
119		tetraethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))dimalonate	877
120		2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))dimalonic acid	765
121		diethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))diacetate	733
122		2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))diacetic acid	677
123		diethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))(2S,2'S)-dipropionate	761
124		(2S,2'S)-2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))dipropionic acid	705
125		diethyl 2,2'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))diisobutyrate	817

		diyl))bis(methylene))bis(azane diyl))(2 <i>S</i> ,2' <i>S</i>)-bis(3-methylbutanoate)	
126		(2 <i>S</i> ,2' <i>S</i>)-2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azanediyl))bis(3-methylbutanoic acid)	761
127		diethyl 1,1'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(cyclopropane-1-carboxylate)	785
128		1,1'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(azane diyl))bis(cyclopropane-1-carboxylic acid)	729
129		diethyl 2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(methylazanediyl))diacetate	761
130		2,2'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))bis(methylazanediyl))diacetic acid	705
131		dimethyl 1,1'-((((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl))bis(azanediyl))bis(carbonyl))bis(4-cyclopropylpyridine-6,3-diyl))bis(methylene))(3 <i>R</i> ,3' <i>R</i>)-bis(pyrrolidine-3-carboxylate)	785

132		(3 <i>R</i> ,3' <i>R</i>)-1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-cyclopropylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (pyrrolidine-3-carboxylic acid)	757
133		dimethyl 1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-cyclopropylpyridine-6,3-diyl)) <i>bis</i> (methylene))(3 <i>S</i> ,3' <i>S</i>)- <i>bis</i> (pyrrolidine-3-carboxylate)	785
134		(3 <i>S</i> ,3' <i>S</i>)-1,1'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-cyclopropylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (pyrrolidine-3-carboxylic acid)	757
135		diethyl 4,4'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-cyclopropylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azane diyl))(3 <i>S</i> ,3' <i>S</i>)- <i>bis</i> (3-hydroxybutanoate)	821
136		(3 <i>S</i> ,3' <i>S</i>)-4,4'-((((2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (azanediyl)) <i>bis</i> (carbonyl)) <i>bis</i> (4-cyclopropylpyridine-6,3-diyl)) <i>bis</i> (methylene)) <i>bis</i> (azanediyl)) <i>bis</i> (3-hydroxybutanoic acid)	765
137		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-((((<i>S</i>)-5-oxopyrrolidin-2-yl)methyl)amino)methyl)picolinamide)	755
138		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((2-fluoroethyl)amino)methyl)picolinamide)	653

139		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((2,2-difluoroethyl)amino)methyl)picolinamide)	689
140		<i>N,N'</i> -(2,2'-dimethyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (4-cyclopropyl-5-(((2,2,2-trifluoroethyl)amino)methyl)picolinamide)	725
141		<i>N,N'</i> -(2-chloro-2'-methyl-[1,1'-biphenyl]-3,3'-diyl) <i>bis</i> (5-(((2-hydroxyethyl)amino)methyl)-4-methoxypicolinamide)	649

¹H NMR data of the compound prepared in the above example are as follows:

Exempl e No.	¹ H-NMR
3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.39 (s, 2H), 8.54 (s, 2H), 7.90 (d, <i>J</i> = 7.9 Hz, 2H), 7.76 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.4 Hz, 2H), 4.00 (s, 6H), 3.85 (s, 4H), 3.51 (t, <i>J</i> = 5.6 Hz, 4H), 2.65 (t, <i>J</i> = 5.6 Hz, 4H), 2.02 (s, 6H).
4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.52 (s, 2H), 7.92 (d, <i>J</i> = 8.1 Hz, 2H), 7.74 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.6 Hz, 2H), 4.87 (brs, 2H), 3.98 (s, 6H), 3.85 (d, <i>J</i> = 14.8 Hz, 2H), 3.72 (d, <i>J</i> = 14.9 Hz, 2H), 3.59 (s, 6H), 3.58 (d, <i>J</i> = 5.8 Hz, 4H), 3.30 (d, <i>J</i> = 5.8 Hz, 2H), 2.02 (s, 6H).
5	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 2H), 8.58 (s, 2H), 7.98 (s, 2H), 7.94 – 7.86 (m, 2H), 7.33 (t, <i>J</i> = 7.9 Hz, 2H), 6.99 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.54 (t, <i>J</i> = 5.4 Hz, 2H), 3.83 (s, 4H), 3.49 (q, <i>J</i> = 5.6 Hz, 4H), 2.62 (t, <i>J</i> = 5.8 Hz, 4H), 2.45 (s, 6H), 2.02 (s, 6H).
7	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.57 (s, 2H), 7.98 (s, 2H), 7.92 (d, <i>J</i> = 7.9 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.5 Hz, 2H), 3.82 (s, 4H), 3.43 (t, <i>J</i> = 5.6 Hz, 4H), 3.25 (s, 6H), 2.71 (t, <i>J</i> = 5.6 Hz, 4H), 2.44 (s, 6H), 2.02 (s, 6H).
8	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.23 (s, 2H), 8.52 (s, 2H), 7.88 (s, 2H), 7.83 (d, <i>J</i> = 7.9 Hz, 2H), 7.23 (t, <i>J</i> = 7.8 Hz, 2H), 6.89 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 3.80 (s, 4H), 3.54 – 3.42 (m, 4H), 3.35 (dd, <i>J</i> = 10.8, 5.6 Hz, 2H), 3.29 (dd, <i>J</i> = 10.8, 5.5 Hz, 2H), 2.93 (brs, 2H), 2.48 (p, <i>J</i> = 5.7 Hz, 2H), 2.36 (s, 6H), 1.92 (s, 6H).
10	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.61 (s, 2H), 7.98 (s, 2H), 7.92 (d, <i>J</i> = 8.0 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.5 Hz, 2H), 5.19 (s, 2H), 3.88 (s, 4H), 2.66 (s, 4H), 2.45 (s, 6H), 2.02 (s, 6H), 0.60 – 0.52 (m, 4H), 0.49 – 0.40 (m, 4H).
11	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.31 (s, 2H), 8.49 (s, 2H), 7.99 (s, 2H), 7.92 (d, <i>J</i> = 8.0 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.6 Hz, 2H), 5.21 (s, 2H), 3.70 (s, 4H), 3.21 (d, <i>J</i> = 6.5 Hz, 4H), 2.97 (d, <i>J</i> = 6.5 Hz, 4H),

	2.43 (s, 6H), 2.02 (s, 6H), 1.37 (s, 6H).
13	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.53 (s, 2H), 8.00 (s, 2H), 7.93 (d, <i>J</i> = 8.0 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.5 Hz, 2H), 4.72 (d, <i>J</i> = 4.4 Hz, 2H), 4.25 – 4.16 (m, 2H), 3.72 (d, <i>J</i> = 13.6 Hz, 2H), 3.65 (d, <i>J</i> = 13.6 Hz, 2H), 2.70 (dd, <i>J</i> = 9.6, 6.1 Hz, 2H), 2.63 (q, <i>J</i> = 7.7 Hz, 2H), 2.46 (s, 6H), 2.45 – 2.40 (m, 2H), 2.36 (dd, <i>J</i> = 9.6, 3.6 Hz, 2H), 2.03 (s, 6H), 2.05 – 1.95 (m, 2H), 1.62 – 1.51 (m, 2H).
14	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 2H), 8.54 (s, 2H), 8.02 (s, 2H), 7.90 (d, <i>J</i> = 8.1 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.6 Hz, 2H), 3.76 (s, 4H), 2.92 (t, <i>J</i> = 13.2 Hz, 4H), 2.74 (t, <i>J</i> = 7.0 Hz, 4H), 2.47 (s, 6H), 2.27 (tt, <i>J</i> = 14.9, 6.9 Hz, 4H), 2.02 (s, 6H).
15	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.55 (s, 2H), 7.98 (s, 2H), 7.93 (dd, <i>J</i> = 8.1, 1.2 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (dd, <i>J</i> = 7.5, 1.3 Hz, 2H), 3.85 (s, 4H), 2.45 (s, 6H), 2.10 (tt, <i>J</i> = 6.7, 3.6 Hz, 2H), 2.02 (s, 6H), 0.38 (dt, <i>J</i> = 6.1, 3.0 Hz, 4H), 0.31 – 0.19 (m, 4H).
16	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.57 (s, 2H), 7.98 (s, 2H), 7.92 (dd, <i>J</i> = 8.1, 1.2 Hz, 2H), 7.82 (t, <i>J</i> = 5.5 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 3.80 (s, 4H), 3.16 (q, <i>J</i> = 6.3 Hz, 4H), 2.59 (t, <i>J</i> = 6.5 Hz, 4H), 2.45 (s, 6H), 2.02 (s, 6H), 1.79 (s, 6H).
17	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.35 (s, 2H), 8.54 (s, 2H), 8.03 (s, 2H), 7.90 (dd, <i>J</i> = 8.1, 1.2 Hz, 2H), 7.80 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 3.67 (s, 4H), 3.14 (t, <i>J</i> = 6.2 Hz, 4H), 2.98 (s, 4H), 2.58 (t, <i>J</i> = 5.5 Hz, 4H), 2.49 (s, 6H), 2.02 (s, 6H).
18	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 2H), 8.62 (s, 2H), 7.99 (s, 2H), 7.92 (d, <i>J</i> = 8.0 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (dd, <i>J</i> = 7.7, 1.3 Hz, 2H), 3.93 (d, <i>J</i> = 14.0 Hz, 2H), 3.84 (d, <i>J</i> = 14.0 Hz, 2H), 3.76 (ddd, <i>J</i> = 20.6, 9.8, 4.3 Hz, 4H), 3.26 (ddd, <i>J</i> = 11.2, 8.1, 3.2 Hz, 4H), 2.96 (t, <i>J</i> = 10.2 Hz, 2H), 2.46 (s, 6H), 2.02 (s, 6H), 2.00 – 1.91 (m, 2H), 1.28 (qd, <i>J</i> = 12.6, 4.4 Hz, 2H).
19	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.57 (s, 2H), 7.97 (s, 2H), 7.92 (dd, <i>J</i> = 8.1, 1.3 Hz, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.6, 1.4 Hz, 2H), 3.81 (s, 4H), 3.37 (dq, <i>J</i> = 10.0, 4.6 Hz, 2H), 2.44 (s, 6H), 2.42 – 2.36 (m, 2H), 2.02 (s, 6H), 1.91 (d, <i>J</i> = 11.0 Hz, 4H), 1.80 (d, <i>J</i> = 10.9 Hz, 4H), 1.24 – 1.01 (m, 8H).
20	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.56 (s, 2H), 7.99 (s, 2H), 7.92 (d, <i>J</i> = 8.1 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.5 Hz, 2H), 4.87 (t, <i>J</i> = 5.8 Hz, 2H), 3.91 (d, <i>J</i> = 13.9 Hz, 2H), 3.74 (d, <i>J</i> = 13.9 Hz, 2H), 3.64 (s, 6H), 3.60 (t, <i>J</i> = 5.6 Hz, 4H), 2.45 (s, 6H), 2.02 (s, 6H).
21	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.60 (s, 2H), 7.99 (s, 2H), 7.91 (d, <i>J</i> = 8.0 Hz, 2H), 7.32 (t, <i>J</i> = 7.7 Hz, 2H), 6.98 (d, <i>J</i> = 7.6 Hz, 2H), 3.97 (d, <i>J</i> = 13.8 Hz, 2H), 3.82 (d, <i>J</i> = 14.0 Hz, 2H), 3.56 (d, <i>J</i> = 5.3 Hz, 4H), 3.09 (brs, 2H), 2.46 (s, 6H), 2.01 (s, 6H).
22	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.56 (s, 2H), 7.98 (s, 2H), 7.91 (d, <i>J</i> = 7.9 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.88 (t, <i>J</i> = 5.8 Hz, 2H), 3.91 (d, <i>J</i> = 13.9 Hz, 2H), 3.74 (d, <i>J</i> = 13.9 Hz, 2H), 3.64 (s, 6H), 3.61 (t, <i>J</i> = 5.4 Hz, 4H), 2.45 (s, 6H), 2.02 (s, 6H).
23	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 2H), 8.61 (s, 2H), 8.00 (s, 2H), 7.90 (d, <i>J</i> = 8.0 Hz, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.5 Hz, 2H),

	4.01 (d, $J = 13.9$ Hz, 2H), 3.86 (d, $J = 13.8$ Hz, 2H), 3.63 (t, $J = 4.6$ Hz, 2H), 3.21 (t, $J = 5.3$ Hz, 2H), 2.47 (s, 6H), 2.02 (s, 6H).
24	^1H NMR (400 MHz, DMSO- d_6) δ 10.33 (s, 2H), 8.55 (s, 2H), 7.99 (s, 2H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.33 (t, $J = 7.9$ Hz, 2H), 6.99 (d, $J = 7.5$ Hz, 2H), 3.84 (s, 4H), 3.64 (s, 6H), 3.41 (s, 4H), 2.45 (s, 6H), 2.02 (s, 6H).
25	^1H NMR (400 MHz, DMSO- d_6) δ 10.35 (s, 2H), 8.62 (s, 2H), 8.01 (s, 2H), 7.88 (d, $J = 8.0$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 3.97 (s, 4H), 3.27 (s, 4H), 2.48 (s, 6H), 2.02 (s, 6H).
27	^1H NMR (400 MHz, DMSO- d_6) δ 10.34 (s, 2H), 8.54 (s, 2H), 7.99 (s, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.5$ Hz, 2H), 3.89 (d, $J = 13.9$ Hz, 2H), 3.60 (d, $J = 13.8$ Hz, 2H), 3.19 (t, $J = 4.3$ Hz, 2H), 2.89 – 2.76 (m, 2H), 2.47 (s, 6H), 2.29 – 2.18 (m, 2H), 2.02 (s, 6H), 1.76 (brs, 4H), 1.44 (brs, 8H).
28	^1H NMR (400 MHz, DMSO- d_6) δ 10.32 (s, 2H), 8.51 (s, 2H), 7.99 (s, 2H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.4$ Hz, 2H), 3.81 (d, $J = 14.0$ Hz, 2H), 3.65 (s, 6H), 3.59 (d, $J = 14.0$ Hz, 2H), 2.84 – 2.76 (m, 2H), 2.46 (s, 6H), 2.30 – 2.21 (m, 2H), 2.02 (s, 6H), 2.00 – 1.94 (m, 2H), 1.82 – 1.71 (m, 4H), 1.48 – 1.41 (m, 8H).
29	^1H NMR (400 MHz, DMSO- d_6) δ 10.32 (s, 2H), 8.54 (s, 2H), 7.97 (s, 2H), 7.92 (d, $J = 8.2$ Hz, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (d, $J = 6.9$ Hz, 2H), 3.91 (d, $J = 14.0$ Hz, 2H), 3.56 (d, $J = 13.9$ Hz, 2H), 3.12 (brs, 2H), 2.89 – 2.78 (m, 2H), 2.47 (s, 6H), 2.26 – 2.14 (m, 2H), 2.02 (s, 6H), 1.78 – 1.73 (m, 4H), 1.48 – 1.40 (m, 8H).
30	^1H NMR (400 MHz, DMSO- d_6) δ 10.36 (s, 2H), 8.67 (s, 2H), 8.01 (s, 2H), 7.88 (d, $J = 8.3$ Hz, 2H), 7.33 (t, $J = 9.4$ Hz, 2H), 6.99 (d, $J = 7.2$ Hz, 2H), 4.05 (d, $J = 15.8$ Hz, 2H), 3.92 (d, $J = 15.7$ Hz, 2H), 3.62 – 3.49 (m, 4H), 2.50 (s, 6H), 2.02 (s, 6H), 1.85 (brs, 4H).
31	^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (s, 2H), 8.50 (s, 2H), 7.91 (d, $J = 7.8$ Hz, 2H), 7.77 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (dd, $J = 7.6, 1.3$ Hz, 2H), 3.99 (s, 6H), 3.58 (t, $J = 4.6$ Hz, 8H), 3.57 (s, 4H), 2.42 (t, $J = 4.6$ Hz, 8H), 2.02 (s, 6H).
32	^1H NMR (400 MHz, DMSO- d_6) δ 10.39 (s, 2H), 8.50 (s, 2H), 7.89 (d, $J = 8.0$ Hz, 2H), 7.75 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 3.99 (s, 6H), 3.76 (s, 4H), 2.32 (s, 6H), 2.02 (s, 6H).
33	^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (s, 2H), 8.52 (s, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.76 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.6$ Hz, 2H), 4.00 (s, 6H), 3.82 (s, 4H), 3.60 – 3.55 (m, 2H), 3.35 – 3.25 (m, 4H), 2.65 (dd, $J = 11.9, 4.2$ Hz, 2H), 2.50 – 2.45 (m, 2H), 2.03 (s, 6H).
34	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.51 (s, 2H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.75 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.4$ Hz, 2H), 3.99 (s, 6H), 3.80 (s, 4H), 3.40 (m, 4H), 3.24 (s, 6H), 2.69 (t, $J = 5.6$ Hz, 4H), 2.02 (s, 6H).
35	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.51 (s, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.75 (s, 2H), 7.33 (t, $J = 7.9$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 6.67 (t, $J = 76.4$ Hz, 2H), 3.99 (s, 6H), 3.89 (t, $J = 5.7$ Hz, 4H), 3.79 (s, 4H), 2.75 (t, $J = 5.7$ Hz, 4H), 2.02 (s, 6H). ^{19}F NMR (376 MHz, DMSO) δ -82.13.
36	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.49 (s, 2H), 7.88 (d, $J =$

	8.0 Hz, 2H), 7.74 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 3.97 (s, 6H), 3.61 (s, 4H), 3.23 (s, 6H), 2.57 (t, $J = 6.0$ Hz, 4H), 2.22 (s, 6H), 2.01 (s, 6H).
37	^1H NMR (400 MHz, DMSO- d_6) δ 10.39 (s, 2H), 8.55 (s, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.76 (s, 2H), 7.34 (t, $J = 7.9$ Hz, 2H), 7.00 (d, $J = 7.6$ Hz, 2H), 3.99 (s, 6H), 3.61 (s, 4H), 3.53 (t, $J = 6.3$ Hz, 4H), 2.48 (t, $J = 6.3$ Hz, 4H), 2.22 (s, 6H), 2.03 (s, 6H).
38	^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (s, 2H), 8.52 (s, 2H), 7.91 (d, $J = 8.2$ Hz, 2H), 7.75 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 4.07 (t, $J = 5.8$ Hz, 4H), 3.99 (s, 6H), 3.79 (s, 4H), 2.74 (t, $J = 5.8$ Hz, 4H), 2.03 (s, 6H), 2.01 (s, 6H).
39	^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (s, 2H), 8.52 (s, 2H), 7.90 (d, $J = 8.2$ Hz, 2H), 7.88 – 7.84 (m, 2H), 7.76 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 4.00 (s, 6H), 3.83 (s, 4H), 3.17 (q, $J = 6.2$ Hz, 4H), 2.62 (t, $J = 6.4$ Hz, 4H), 2.02 (s, 6H), 1.80 (s, 6H).
40	^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (3, 2H), 8.56 (s, 2H), 7.89 (d, $J = 8.0$ Hz, 2H), 7.77 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.6$ Hz, 2H), 4.01 (s, 6H), 3.92 (s, 4H), 2.02 (s, 6H), 1.12 (s, 12H).
41	^1H NMR (400 MHz, DMSO- d_6) δ 10.39 (s, 2H), 8.57 (s, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.77 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.01 (d, $J = 7.5$ Hz, 2H), 4.01 (s, 6H), 3.91 (s, 4H), 2.69 (s, 4H), 2.03 (s, 6H), 0.62 – 0.52 (m, 4H), 0.50 – 0.41 (m, 4H).
42	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.54 (s, 2H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.75 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.5$ Hz, 2H), 3.99 (s, 6H), 3.88 (d, $J = 14.7$ Hz, 2H), 3.81 (d, $J = 14.7$ Hz, 2H), 3.35 – 3.18 (m, 4H), 2.65 (q, $J = 6.1$ Hz, 2H), 2.02 (s, 6H), 0.98 (d, $J = 6.3$ Hz, 6H).
43	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.54 (s, 2H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.75 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 3.99 (s, 6H), 3.86 (d, $J = 14.8$ Hz, 2H), 3.79 (d, $J = 14.8$ Hz, 2H), 3.29 (qd, $J = 10.6, 5.8$ Hz, 4H), 2.62 (dq, $J = 13.0, 6.6$ Hz, 2H), 2.03 (s, 6H), 0.97 (d, $J = 6.3$ Hz, 6H).
44	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.52 (s, 2H), 7.93 (d, $J = 8.2$ Hz, 2H), 7.74 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 3.99 (s, 6H), 3.79 (brs, 6H), 2.78 – 2.69 (m, 2H), 2.03 (s, 6H), 1.94 – 1.72 (m, 4H), 1.66 – 1.51 (m, 4H), 1.40 (dq, $J = 12.7, 6.0$ Hz, 2H), 1.30 (dq, $J = 13.8, 7.3$ Hz, 2H).
45	^1H NMR (400 MHz, DMSO- d_6) δ 10.36 (s, 2H), 8.41 (s, 2H), 7.89 (d, $J = 8.1$ Hz, 2H), 7.75 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.6$ Hz, 2H), 4.21 (p, $J = 6.2$ Hz, 2H), 3.98 (s, 6H), 3.64 (s, 4H), 3.57 (td, $J = 6.1, 2.1$ Hz, 4H), 2.86 (t, $J = 6.9$ Hz, 4H), 2.02 (s, 6H).
46	^1H NMR (400 MHz, DMSO- d_6) δ 10.35 (s, 2H), 8.41 (s, 2H), 7.92 (d, $J = 8.1$ Hz, 2H), 7.74 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 3.98 (s, 6H), 3.65 (s, 4H), 3.25 (d, $J = 7.3$ Hz, 4H), 2.96 (d, $J = 6.5$ Hz, 4H), 2.02 (s, 6H), 1.37 (s, 6H).
47	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.49 (s, 2H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.75 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 4.20 (tt, $J = 7.1, 3.5$ Hz, 2H), 3.98 (s, 6H), 3.72 – 3.66 (m, 4H), 2.79 – 2.61

	(m, 4H), 2.40 (dd, $J = 9.7, 3.5$ Hz, 4H), 2.08 – 1.91 (m, 8H), 1.55 (qd, $J = 8.1, 3.7$ Hz, 2H).
48	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.49 (s, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.75 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 4.20 (tt, $J = 7.0, 3.5$ Hz, 2H), 3.98 (s, 6H), 3.71 (d, $J = 14.2$ Hz, 2H), 3.65 (d, $J = 14.2$ Hz, 2H), 2.81 – 2.60 (m, 4H), 2.41 (dd, $J = 9.8, 3.5$ Hz, 4H), 2.08 – 1.91 (m, 8H), 1.60 – 1.51 (m, 2H).
49	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.47 (s, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.75 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.6$ Hz, 2H), 3.98 (s, 6H), 3.54 (s, 4H), 2.70 (dd, $J = 10.8, 5.5$ Hz, 4H), 2.12 (t, $J = 10.5$ Hz, 4H), 2.03 (s, 6H), 1.80 – 1.64 (m, 4H), 1.50 – 1.31 (m, 4H).
50	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.47 (s, 2H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.76 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 3.99 (s, 6H), 3.94 – 3.84 (m, 2H), 3.68 (d, $J = 14.2$ Hz, 2H), 3.64 (d, $J = 14.0$ Hz, 2H), 3.15 (s, 6H), 2.72 (dd, $J = 10.0, 6.2$ Hz, 2H), 2.60 (q, $J = 7.8$ Hz, 2H), 2.49 – 2.42 (m, 4H), 2.02 (s, 6H), 2.01 – 1.91 (m, 2H), 1.71 – 1.60 (m, 2H).
51	^1H NMR (400 MHz, DMSO- d_6) δ 10.36 (s, 2H), 8.41 (s, 2H), 7.89 (d, $J = 8.1$ Hz, 2H), 7.74 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.6$ Hz, 2H), 3.98 (s, 6H), 3.64 (s, 4H), 3.53 (dd, $J = 7.9, 5.9$ Hz, 4H), 3.15 (s, 6H), 2.91 (dd, $J = 7.7, 5.6$ Hz, 4H), 2.02 (s, 6H).
52	^1H NMR (400 MHz, DMSO- d_6) δ 10.35 (s, 2H), 8.42 (s, 2H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.74 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 4.00 – 3.96 (m, 8H), 3.66 (s, 4H), 3.20 – 3.15 (m, 4H), 3.10 (s, 6H), 3.08 – 2.98 (m, 4H), 2.02 (s, 6H), 1.39 (s, 6H).
53	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.48 (s, 2H), 7.91 (d, $J = 8.3$ Hz, 2H), 7.73 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.8$ Hz, 2H), 3.99 (s, 6H), 3.79 – 3.64 (m, 6H), 2.43 – 2.35 (m, 2H), 2.02 (s, 6H), 1.61 – 1.44 (m, 4H), 1.19 – 0.95 (m, 4H).
54	^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (s, 2H), 8.48 (s, 2H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.74 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 4.57 (t, $J = 6.5$ Hz, 4H), 4.28 (t, $J = 6.1$ Hz, 4H), 4.00 (s, 6H), 3.90 (p, $J = 6.6$ Hz, 2H), 3.69 (s, 4H), 2.02 (s, 6H).
55	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.52 (s, 2H), 7.92 (d, $J = 8.1$ Hz, 2H), 7.74 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 3.99 (s, 6H), 3.82 – 3.59 (m, 10H), 3.46 – 3.44 (m, 2H), 3.33 – 3.23 (m, 2H), 2.02 (s, 6H), 2.02 – 1.88 (m, 2H), 1.76 – 1.63 (m, 2H).
56	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.52 (s, 2H), 7.92 (d, $J = 8.0$ Hz, 2H), 7.74 (s, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 3.99 (s, 6H), 3.81 – 3.61 (m, 10H), 3.46 – 3.44 (m, 2H), 3.34 – 3.23 (m, 2H), 2.02 (s, 6H), 2.02 – 1.88 (m, 2H), 1.77 – 1.63 (m, 2H).
57	^1H NMR (400 MHz, DMSO- d_6) δ 10.36 (s, 2H), 8.48 (s, 2H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.76 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.5$ Hz, 2H), 4.85 (d, $J = 7.2$ Hz, 4H), 4.54 (d, $J = 7.2$ Hz, 4H), 4.00 (s, 6H), 3.86 (s, 4H), 3.06 (t, $J = 6.8$ Hz, 4H), 2.31 (t, $J = 6.8$ Hz, 4H), 2.02 (s, 6H).
58	^1H NMR (400 MHz, DMSO- d_6) δ 10.35 (s, 2H), 8.39 (s, 2H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.74 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 4.61 (s, 8H), 3.98 (s, 6H), 3.56 (s, 4H), 2.02 (s, 6H).

59	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.52 (s, 2H), 7.90 (d, <i>J</i> = 8.1 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 3.99 (s, 6H), 3.96 – 3.87 (m, 2H), 3.87 – 3.75 (m, 4H), 2.58 – 2.51 (m, 4H), 2.40 (dd, <i>J</i> = 15.2, 5.2 Hz, 2H), 2.23 (dd, <i>J</i> = 15.1, 7.3 Hz, 2H), 2.02 (s, 6H).
60	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.49 (s, 2H), 7.91 (d, <i>J</i> = 8.0 Hz, 2H), 7.73 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.5 Hz, 2H), 3.99 (s, 6H), 3.69 (s, 4H), 3.09 (p, <i>J</i> = 7.7 Hz, 2H), 2.59 (dt, <i>J</i> = 16.9, 8.0 Hz, 2H), 2.34 – 2.20 (m, 4H), 2.02 (s, 6H), 1.89 – 1.71 (m, 4H).
61	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.57 (s, 2H), 7.91 (d, <i>J</i> = 8.1 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.9 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 4.07 (d, <i>J</i> = 14.4 Hz, 2H), 3.98 (s, 6H), 3.85 (d, <i>J</i> = 14.5 Hz, 2H), 3.28 – 3.19 (m, 2H), 3.11 – 3.02 (m, 2H), 2.02 (s, 6H), 1.95 – 1.79 (m, 2H), 1.80 – 1.65 (m, 4H).
62	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.55 (s, 2H), 7.93 (d, <i>J</i> = 8.1 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 4.21 (brs, 2H), 3.99 (d, <i>J</i> = 14.7 Hz, 2H), 3.98 (s, 6H), 3.83 (d, <i>J</i> = 14.7 Hz, 2H), 3.22 (t, <i>J</i> = 7.5 Hz, 4H), 2.31 (brd, <i>J</i> = 10.1 Hz, 2H), 2.03 (brs, 8H), 1.90 – 1.88 (m, 2H).
63	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.59 (s, 2H), 7.94 (d, <i>J</i> = 8.1 Hz, 2H), 7.74 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.8 Hz, 2H), 3.97 (s, 6H), 3.85 – 3.70 (m, 4H), 3.65 – 3.55 (m, 4H), 3.19 (brs, 2H), 2.99 (brs, 2H), 2.32 – 2.24 (m, 2H), 2.03 (s, 6H).
64	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.51 (s, 2H), 7.92 (d, <i>J</i> = 8.1 Hz, 2H), 7.74 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.96 (s, 6H), 3.78 – 3.58 (m, 10H), 2.91 (dt, <i>J</i> = 11.3, 5.5 Hz, 2H), 2.30 (dt, <i>J</i> = 11.4, 5.4 Hz, 2H), 2.03 (s, 6H), 1.76 (dt, <i>J</i> = 13.0, 6.1 Hz, 4H), 1.55 – 1.45 (m, 4H), 1.45 – 1.35 (m, 4H).
65	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.58 (s, 2H), 7.94 (d, <i>J</i> = 8.1 Hz, 2H), 7.73 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.97 (s, 6H), 3.83 (d, <i>J</i> = 15.3 Hz, 2H), 3.68 (d, <i>J</i> = 15.3 Hz, 2H), 3.11 (brs, 2H), 2.97 – 2.89 (m, 2H), 2.23 (brs, 2H), 2.04 (s, 6H), 1.76 (brs, 4H), 1.50 (brs, 6H), 1.36 (brs, 2H).
66	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.50 (s, 2H), 7.90 (dd, <i>J</i> = 8.2, 1.3 Hz, 2H), 7.74 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 3.98 (s, 6H), 3.79 (s, 4H), 3.62 (s, 6H), 3.38 (s, 4H), 2.02 (s, 6H).
67	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.55 (s, 2H), 7.87 (d, <i>J</i> = 8.3 Hz, 2H), 7.78 (s, 2H), 7.34 (t, <i>J</i> = 7.9 Hz, 2H), 7.01 (d, <i>J</i> = 7.6 Hz, 2H), 4.01 (s, 10H), 3.19 (s, 4H), 2.02 (s, 6H).
68	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.55 (s, 2H), 7.92 (d, <i>J</i> = 8.1 Hz, 2H), 7.76 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 4.33 (td, <i>J</i> = 8.6, 2.5 Hz, 2H), 4.16 (td, <i>J</i> = 9.2, 6.2 Hz, 2H), 4.01 (s, 6H), 3.98 – 3.85 (m, 4H), 3.58 (dd, <i>J</i> = 9.9, 8.1 Hz, 2H), 2.49 – 2.38 (m, 2H), 2.11 – 1.94 (m, 8H).
69	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.54 (s, 2H), 7.88 (d, <i>J</i> = 7.9 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.9 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 3.99 (s, 6H), 3.99 – 3.93 (m, 2H), 3.83 (d, <i>J</i> = 15.0 Hz, 2H), 3.23 – 3.15 (m,

	2H), 2.02 (s, 6H), 1.80 (brs, 2H), 1.71 (brs, 2H).
70	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.54 (s, 2H), 7.91 (d, <i>J</i> = 8.0 Hz, 2H), 7.75 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 4.32 (td, <i>J</i> = 8.5, 2.5 Hz, 2H), 4.15 (td, <i>J</i> = 9.3, 6.3 Hz, 2H), 4.00 (s, 6H), 3.98 – 3.85 (m, 4H), 3.57 (t, <i>J</i> = 9.1 Hz, 2H), 2.48 – 2.39 (m, 2H), 2.05 – 2.95 (m, 8H).
71	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.54 (s, 2H), 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.75 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 3.99 (s, 6H), 3.93 (d, <i>J</i> = 14.6 Hz, 2H), 3.80 (d, <i>J</i> = 14.8 Hz, 2H), 3.63 – 3.47 (m, 4H), 3.26 – 3.22 (m, 2H), 2.02 (s, 6H), 1.90 – 1.75 (m, 2H), 1.75 – 1.62 (m, 2H).
72	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.51 (s, 2H), 7.92 (d, <i>J</i> = 8.2 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 4.29 (dd, <i>J</i> = 9.4, 5.2 Hz, 2H), 4.13 (d, <i>J</i> = 9.2 Hz, 2H), 4.00 (s, 6H), 3.86 – 3.70 (m, 4H), 3.51 – 3.48 (m, 2H), 2.72 (dd, <i>J</i> = 17.4, 6.8 Hz, 2H), 2.34 (d, <i>J</i> = 16.9 Hz, 2H), 2.02 (s, 6H).
73	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.54 (s, 2H), 7.90 (d, <i>J</i> = 8.0 Hz, 2H), 7.76 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 3.99 (s, 6H), 3.97 – 3.78 (m, 4H), 2.94 – 2.88 (m, 4H), 2.28 (tt, <i>J</i> = 15.8, 8.3 Hz, 4H), 2.02 (s, 6H).
74	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.51 (s, 2H), 7.91 (d, <i>J</i> = 8.1 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 4.30 (dd, <i>J</i> = 9.4, 5.3 Hz, 2H), 4.13 (dd, <i>J</i> = 9.3, 2.7 Hz, 2H), 4.00 (s, 6H), 3.84 – 3.69 (m, 4H), 3.55 – 3.25 (m), 2.72 (dd, <i>J</i> = 17.3, 6.8 Hz, 2H), 2.34 (dd, <i>J</i> = 17.3, 3.0 Hz, 2H), 2.02 (s, 6H).
75	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.54 (s, 2H), 7.91 (d, <i>J</i> = 8.0 Hz, 2H), 7.75 (s, 2H), 7.33 (t, <i>J</i> = 7.7 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 3.99 (s, 6H), 3.95 – 3.81 (m, 4H), 3.49 – 3.30 (m), 2.89 (brs, 2H), 2.27 (t, <i>J</i> = 7.7 Hz, 4H), 2.02 (s, 6H).
76	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.50 (s, 2H), 7.91 (d, <i>J</i> = 8.1 Hz, 2H), 7.73 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.98 (s, 6H), 3.85 (d, <i>J</i> = 14.9 Hz, 2H), 3.73 (d, <i>J</i> = 14.9 Hz, 2H), 3.59 (s, 6H), 3.56 – 3.50 (m, 4H), 3.49 – 3.43 (m, 2H), 3.23 (s, 6H), 2.02 (s, 6H).
77	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.53 (s, 2H), 7.90 (d, <i>J</i> = 8.1 Hz, 2H), 7.75 (s, 2H), 7.33 (t, <i>J</i> = 7.9 Hz, 2H), 7.00 (d, <i>J</i> = 7.4 Hz, 2H), 3.99 (s, 6H), 3.98 – 3.80 (m, 4H), 3.56 (t, <i>J</i> = 4.6 Hz, 4H), 2.02 (s, 6H).
78	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.50 (s, 2H), 7.91 (d, <i>J</i> = 8.1 Hz, 2H), 7.73 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.6 Hz, 2H), 3.98 (s, 6H), 3.85 (d, <i>J</i> = 14.9 Hz, 2H), 3.79 – 3.63 (m, 4H), 3.59 (s, 6H), 3.59 – 3.42 (m, 4H), 3.23 (s, 6H), 2.84 (q, <i>J</i> = 7.3 Hz, 2H), 2.02 (s, 6H).
79	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.54 (s, 2H), 7.89 (d, <i>J</i> = 7.9 Hz, 2H), 7.75 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.7 Hz, 2H), 4.00 (s, 6H), 3.98 – 3.83 (m, 4H), 3.57 (d, <i>J</i> = 5.1 Hz, 4H), 3.24 (s, 6H), 2.02 (s, 6H).
80	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.51 (s, 2H), 7.90 (d, <i>J</i> = 8.0 Hz, 2H), 7.76 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 3.99 (s, 6H), 3.79 (s, 4H), 3.27 (t, <i>J</i> = 6.6 Hz, 4H), 3.02 (s, 6H), 2.93 (t, <i>J</i> = 6.6 Hz, 4H), 2.02 (s, 6H).

82	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.26 (s, 2H), 8.38 (s, 2H), 7.79 (d, <i>J</i> = 8.1 Hz, 2H), 7.65 (s, 2H), 7.23 (t, <i>J</i> = 7.8 Hz, 2H), 6.89 (d, <i>J</i> = 7.5 Hz, 2H), 3.88 (s, 6H), 3.60 – 3.35 (m), 3.00 – 2.88 (m, 2H), 2.68 – 2.56 (m, 4H), 2.47 (t, <i>J</i> = 6.9 Hz, 4H), 1.92 (s, 6H), 1.91 – 1.76 (m, 4H).
83	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.48 (s, 2H), 7.90 (d, <i>J</i> = 8.0 Hz, 2H), 7.75 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.98 (s, 6H), 3.77 – 3.63 (m), 2.98 – 2.79 (m, 2H), 2.79 – 2.64 (m, 4H), 2.56 (brs, 4H), 2.02 (s, 6H), 1.95 (q, <i>J</i> = 7.8, 7.4 Hz, 4H).
84	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.47 (s, 2H), 7.90 (d, <i>J</i> = 8.0 Hz, 2H), 7.76 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.98 (s, 6H), 3.59 (s, 6H), 3.56 (s, 4H), 2.79 (d, <i>J</i> = 11.6 Hz, 4H), 2.38 – 2.24 (m, 2H), 2.09 (t, <i>J</i> = 11.4 Hz, 4H), 2.03 (s, 6H), 1.85 – 1.74 (m, 4H), 1.66 – 1.51 (m, 4H).
86	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.56 (s, 2H), 7.92 (d, <i>J</i> = 8.1 Hz, 2H), 7.75 (s, 2H), 7.41 – 7.28 (m, 4H), 7.11 (d, <i>J</i> = 3.0 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.99 (s, 6H), 3.91 – 3.58 (m), 3.55 (dd, <i>J</i> = 10.7, 4.7 Hz, 2H), 3.44 (dd, <i>J</i> = 10.7, 6.7 Hz, 2H), 3.03 (dd, <i>J</i> = 6.7, 4.7 Hz, 2H), 2.03 (s, 6H).
87	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.54 (s, 2H), 7.91 (d, <i>J</i> = 7.9 Hz, 2H), 7.86 (t, <i>J</i> = 5.8 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.99 (s, 6H), 3.81 – 3.67 (m, 4H), 3.53 (dd, <i>J</i> = 10.7, 4.9 Hz, 4H), 3.17 – 2.99 (m, 8H), 2.03 (s, 6H), 1.00 (t, <i>J</i> = 7.2 Hz, 6H).
88	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.51 (s, 2H), 7.90 (d, <i>J</i> = 8.1 Hz, 2H), 7.75 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 2H), 3.99 (s, 6H), 3.78 (s, 4H), 3.26 – 3.10 (m, 6H), 2.94 (s, 6H), 2.97 – 2.90 (m, 2H), 2.02 (s, 6H).
89	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.51 (s, 2H), 7.91 (dd, <i>J</i> = 8.0, 1.3 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (dd, <i>J</i> = 7.7, 1.3 Hz, 2H), 3.99 (s, 6H), 3.77 (s, 4H), 3.04 (t, <i>J</i> = 6.2 Hz, 4H), 2.98 (s, 12H), 2.59 (t, <i>J</i> = 6.2 Hz, 4H), 2.03 (s, 6H).
90	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 2H), 8.52 (s, 2H), 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.75 (s, 2H), 7.34 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 3.99 (s, 6H), 3.83 (s, 4H), 3.13 (dt, <i>J</i> = 13.0, 6.6 Hz, 4H), 3.08 (t, <i>J</i> = 6.1 Hz, 4H), 2.90 (dt, <i>J</i> = 13.2, 6.8 Hz, 4H), 2.66 (t, <i>J</i> = 6.2 Hz, 4H), 2.16 – 2.05 (m, 4H), 2.02 (s, 6H), 2.05 – 1.94 (m, 4H).
91	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.57 (s, 2H), 7.88 (d, <i>J</i> = 8.0 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.7 Hz, 2H), 6.98 (d, <i>J</i> = 7.4 Hz, 2H), 3.98 (s, 4H), 3.50 (t, <i>J</i> = 5.7 Hz, 4H), 2.65 (t, <i>J</i> = 5.8 Hz, 4H), 2.28 (td, <i>J</i> = 8.2, 4.2 Hz, 2H), 2.00 (s, 6H), 1.19 – 1.08 (m, 4H), 0.89 – 0.80 (m, 4H).
92	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.60 (s, 2H), 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.60 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 2H), 4.04 (s, 4H), 3.50 – 3.35 (m, 8H), 2.61 (p, <i>J</i> = 5.7 Hz, 2H), 2.29 (tq, <i>J</i> = 8.8, 4.4, 3.5 Hz, 2H), 2.01 (s, 6H), 1.16 – 1.10 (m, 4H), 0.86 (q, <i>J</i> = 5.4 Hz, 4H).
93	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.56 (s, 2H), 7.89 (dd, <i>J</i> = 8.2, 1.4 Hz, 2H), 7.81 (t, <i>J</i> = 5.6 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.7, 1.3 Hz, 2H), 3.95 (s, 4H), 3.17 (q, <i>J</i> = 6.2 Hz, 4H), 2.62 (t, <i>J</i> = 6.5 Hz, 4H), 2.28 (ddd, <i>J</i> = 13.7, 8.4, 5.2 Hz, 2H), 2.00 (s, 6H),

	1.79 (s, 6H), 1.17 – 1.07 (m, 4H), 0.89 – 0.79 (m, 4H).
94	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.59 (s, 2H), 7.88 (d, <i>J</i> = 7.8 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 2H), 4.04 (s, 4H), 2.69 (s, 4H), 2.33 – 2.27 (m, 2H), 2.00 (s, 6H), 1.16 – 1.09 (m, 4H), 0.89 – 0.81 (m, 4H), 0.61 – 0.52 (m, 4H), 0.49 – 0.37 (m, 4H).
95	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.57 (s, 2H), 7.87 (d, <i>J</i> = 8.0 Hz, 2H), 7.59 (s, 2H), 7.31 (t, <i>J</i> = 7.8 Hz, 2H), 6.97 (d, <i>J</i> = 7.4 Hz, 2H), 4.00 (s, 4H), 3.74 (q, <i>J</i> = 5.9 Hz, 4H), 2.53 (d, <i>J</i> = 4.4 Hz, 2H), 2.27 (td, <i>J</i> = 8.4, 4.3 Hz, 2H), 2.00 (s, 6H), 1.17 – 1.08 (m, 4H), 1.05 (d, <i>J</i> = 6.1 Hz, 6H), 0.90 – 0.80 (m, 4H).
96	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.58 (s, 2H), 7.88 (d, <i>J</i> = 7.7 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.03 (d, <i>J</i> = 13.8 Hz, 2H), 3.95 (d, <i>J</i> = 13.8 Hz, 2H), 3.36 – 3.24 (m, 4H), 2.69 (h, <i>J</i> = 6.2 Hz, 2H), 2.29 (ddd, <i>J</i> = 13.5, 8.4, 5.1 Hz, 2H), 2.00 (s, 6H), 1.17 – 1.08 (m, 4H), 1.00 (d, <i>J</i> = 6.3 Hz, 6H), 0.91 – 0.79 (m, 4H).
97	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.57 (s, 2H), 7.89 (d, <i>J</i> = 7.9 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.9 Hz, 2H), 6.98 (d, <i>J</i> = 7.2 Hz, 2H), 3.96 (s, 4H), 3.82 (q, <i>J</i> = 4.9 Hz, 2H), 2.82 (q, <i>J</i> = 5.6 Hz, 2H), 2.28 (td, <i>J</i> = 8.3, 4.1 Hz, 2H), 2.00 (s, 6H), 1.91 – 1.77 (m, 4H), 1.62 – 1.52 (m, 4H), 1.46 – 1.38 (m, 2H), 1.38 – 1.28 (m, 2H), 1.12 (d, <i>J</i> = 8.3 Hz, 4H), 0.85 (d, <i>J</i> = 5.1 Hz, 4H).
98	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.31 (s, 2H), 8.47 (s, 2H), 7.86 (d, <i>J</i> = 7.8 Hz, 2H), 7.57 (s, 2H), 7.31 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.22 (p, <i>J</i> = 6.2 Hz, 2H), 3.82 (s, 4H), 3.54 (td, <i>J</i> = 6.1, 2.1 Hz, 4H), 2.91 – 2.83 (m, 4H), 2.31 – 2.21 (m, 2H), 2.00 (s, 6H), 1.17 – 1.09 (m, 4H), 0.90 – 0.81 (m, 4H).
99	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.30 (s, 2H), 8.48 (s, 2H), 7.88 (dd, <i>J</i> = 8.1, 1.3 Hz, 2H), 7.58 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 3.85 (s, 4H), 3.27 – 3.20 (m, 4H), 2.99 (d, <i>J</i> = 6.6 Hz, 4H), 2.31 – 2.22 (m, 2H), 2.00 (s, 6H), 1.38 (s, 6H), 1.18 – 1.09 (m, 4H), 0.88 – 0.81 (m, 4H).
100	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.52 (s, 2H), 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (d, <i>J</i> = 7.6 Hz, 2H), 4.21 (brs, 2H), 3.86 (d, <i>J</i> = 13.5 Hz, 2H), 3.80 (d, <i>J</i> = 13.6 Hz, 2H), 2.75 (dd, <i>J</i> = 9.6, 6.3 Hz, 2H), 2.66 (q, <i>J</i> = 7.6 Hz, 2H), 2.49 – 2.45 (m, 2H), 2.43 – 2.30 (m, 4H), 2.01 (s, 6H), 2.05 – 1.95 (m, 2H), 1.61 – 1.51 (m, 2H), 1.14 (d, <i>J</i> = 8.2 Hz, 4H), 0.85 (d, <i>J</i> = 5.1 Hz, 4H).
101	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.31 (s, 2H), 8.52 (s, 2H), 7.88 (dd, <i>J</i> = 8.2, 1.2 Hz, 2H), 7.58 (s, 2H), 7.31 (t, <i>J</i> = 7.8 Hz, 2H), 6.97 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.21 (dp, <i>J</i> = 9.7, 3.5 Hz, 2H), 3.82 (q, <i>J</i> = 13.5 Hz, 4H), 2.75 (dd, <i>J</i> = 9.6, 6.1 Hz, 2H), 2.66 (q, <i>J</i> = 7.8 Hz, 2H), 2.47 (dd, <i>J</i> = 8.4, 5.5 Hz, 2H), 2.39 (dd, <i>J</i> = 9.6, 3.6 Hz, 2H), 2.34 (tt, <i>J</i> = 8.3, 5.2 Hz, 2H), 2.05 – 1.95 (m, 2H), 2.00 (s, 6H), 1.60 – 1.51 (m, 2H), 1.17 – 1.08 (m, 4H), 0.89 – 0.79 (m, 4H).
102	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.48 (s, 2H), 7.87 (d, <i>J</i> = 8.5 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (d, <i>J</i> = 7.4 Hz, 2H), 3.68 (s, 4H), 3.48 (brs, 2H), 3.09 – 3.03 (m, 2H), 2.75 – 2.67 (m, 4H), 2.38 – 2.31 (m, 2H), 2.18 – 2.10 (m, 2H), 2.00 (s, 6H), 1.82 – 1.75 (m, 2H), 1.74

	– 1.67 (m, 2H), 1.47 – 1.35 (m, 4H), 1.13 (d, $J = 7.8$ Hz, 4H), 0.85 (d, $J = 6.1$ Hz, 4H).
103	^1H NMR (500 MHz, DMSO- d_6) δ 10.40 (s, 2H), 8.60 (s, 2H), 7.96 (d, $J = 8.0$ Hz, 2H), 7.65 (s, 2H), 7.39 (t, $J = 7.8$ Hz, 2H), 7.06 (d, $J = 7.5$ Hz, 2H), 3.93 (s, 4H), 3.87 – 3.77 (m, 2H), 2.77 (ddd, $J = 15.5, 8.2, 6.3$ Hz, 2H), 2.56 – 2.47 (m, 4H), 2.36 (td, $J = 8.4, 4.3$ Hz, 2H), 2.08 (s, 6H), 1.64 (qd, $J = 8.3, 2.9$ Hz, 4H), 1.24 – 1.16 (m, 4H), 0.96 – 0.87 (m, 4H).
104	^1H NMR (500 MHz, DMSO- d_6) δ 10.32 (s, 2H), 8.54 (s, 2H), 7.88 (d, $J = 8.1$ Hz, 2H), 7.59 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (dd, $J = 7.6, 1.3$ Hz, 2H), 4.05 (d, $J = 13.8$ Hz, 2H), 3.88 (d, $J = 13.7$ Hz, 2H), 3.64 (s, 6H), 3.62 (d, $J = 5.2$ Hz, 4H), 3.38 – 3.35 (m, 2H), 2.29 (ddd, $J = 13.6, 8.5, 5.2$ Hz, 2H), 2.00 (s, 6H), 1.13 (dd, $J = 8.3, 2.1$ Hz, 4H), 0.91 – 0.78 (m, 4H).
105	^1H NMR (500 MHz, DMSO- d_6) δ 10.31 (s, 2H), 8.58 (s, 2H), 7.89 (d, $J = 8.2$ Hz, 2H), 7.58 (s, 2H), 7.31 (t, $J = 7.7$ Hz, 2H), 6.97 (d, $J = 7.6$ Hz, 2H), 4.10 (d, $J = 13.7$ Hz, 2H), 3.94 (d, $J = 14.0$ Hz, 2H), 3.52 (d, $J = 5.9$ Hz, 4H), 3.04 – 2.96 (m, 2H), 2.32 (brs, 2H), 2.00 (s, 6H), 1.12 (brs, 4H), 0.85 (brs, 4H).
106	^1H NMR (500 MHz, DMSO- d_6) δ 10.32 (s, 2H), 8.54 (s, 2H), 7.87 (d, $J = 8.1$ Hz, 2H), 7.58 (s, 2H), 7.31 (t, $J = 7.8$ Hz, 2H), 6.98 (dd, $J = 7.6, 1.4$ Hz, 2H), 4.10 (q, $J = 7.1$ Hz, 4H), 4.05 (d, $J = 13.8$ Hz, 2H), 3.89 (d, $J = 13.7$ Hz, 2H), 3.61 (d, $J = 5.2$ Hz, 4H), 3.33 (t, $J = 5.1$ Hz, 2H), 2.34 – 2.25 (m, 2H), 2.00 (s, 6H), 1.19 (t, $J = 7.1$ Hz, 6H), 1.12 (dd, $J = 8.3, 2.0$ Hz, 4H), 0.89 – 0.79 (m, 4H).
107	^1H NMR (500 MHz, DMSO- d_6) δ 10.32 (s, 2H), 8.54 (s, 2H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.59 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (d, $J = 7.5$ Hz, 2H), 4.87 (t, $J = 5.7$ Hz, 2H), 4.10 (q, $J = 7.2$ Hz, 4H), 4.05 (dd, $J = 13.5, 5.0$ Hz, 2H), 3.89 (dd, $J = 13.7, 6.4$ Hz, 2H), 3.61 (t, $J = 5.5$ Hz, 4H), 2.54 (q, $J = 7.1$ Hz, 2H), 2.30 (ddd, $J = 13.6, 8.5, 5.2$ Hz, 2H), 2.00 (s, 6H), 1.20 (t, $J = 7.1$ Hz, 6H), 1.12 (d, $J = 8.7$ Hz, 4H), 0.85 (brs, 4H).
108 (TFA salt)	^1H NMR (500 MHz, DMSO- d_6) δ 10.38 (s, 2H), 8.72 (s, 2H), 7.79 (d, $J = 7.7$ Hz, 2H), 7.64 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 6.9$ Hz, 2H), 4.46 (s, 4H), 4.05 (brs, 2H), 4.00 – 3.94 (m, 2H), 3.91 (dd, $J = 11.8, 4.0$ Hz, 2H), 2.35 (ddd, $J = 13.6, 8.4, 5.1$ Hz, 2H), 2.00 (s, 6H), 1.21 – 1.12 (m, 4H), 0.95 – 0.85 (m, 4H).
109	^1H NMR (500 MHz, DMSO- d_6) δ 10.32 (s, 2H), 8.49 (s, 2H), 7.87 (d, $J = 8.1$ Hz, 2H), 7.59 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (d, $J = 7.6$ Hz, 2H), 3.95 (d, $J = 13.7$ Hz, 2H), 3.70 (d, $J = 13.9$ Hz, 2H), 3.66 (s, 6H), 3.35 – 3.30 (m, 2H), 2.88 – 2.77 (m, 2H), 2.45 – 2.38 (m, 2H), 2.32 – 2.22 (m, 2H), 2.00 (s, 6H), 1.76 (brs, 4H), 1.45 (brs, 8H), 1.12 (d, $J = 8.7$ Hz, 4H), 0.94 – 0.85 (m, 2H), 0.83 – 0.74 (m, 2H).
110 (TFA salt)	^1H NMR (500 MHz, DMSO- d_6) δ 10.34 (s, 2H), 8.59 (s, 2H), 7.84 (d, $J = 8.3$ Hz, 2H), 7.61 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 7.14 (t, $J = 50.0$ Hz, 4H), 6.99 (d, $J = 7.5$ Hz, 2H), 4.40 – 3.00 (m), 2.46 – 2.38 (m, 2H), 2.00 (s, 6H), 2.00 – 1.95 (m, 2H), 1.82 – 1.70 (m, 2H), 1.64 – 1.58 (brs, 6H), 1.50 – 1.42 (brs, 2H), 1.20 – 1.12 (m, 4H), 1.02 – 0.92 (brs, 2H), 0.87 – 0.77 (brs, 2H).
112 (TFA salt)	^1H NMR (500 MHz, DMSO- d_6) δ 10.36 (s, 2H), 8.66 (s, 2H), 7.81 (d, $J = 8.0$ Hz, 2H), 7.62 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.0$ Hz, 2H), 4.34 (brs, 2H), 4.03 (brs, 2H), 3.60 – 3.20 (m), 2.32 (m, 2H), 2.00 (s, 6H),

	1.22 (d, $J = 6.3$ Hz, 6H), 1.15 (d, $J = 8.6$ Hz, 4H), 0.90 (brs, 4H).
113	^1H NMR (500 MHz, DMSO- d_6) δ 10.33 (s, 2H), 8.58 (s, 2H), 7.87 (d, $J = 7.9$ Hz, 2H), 7.60 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (dd, $J = 7.7, 1.3$ Hz, 2H), 4.32 (td, $J = 8.6, 2.5$ Hz, 2H), 4.23 – 4.11 (m, 4H), 4.06 (d, $J = 13.9$ Hz, 2H), 3.64 (t, $J = 9.1$ Hz, 2H), 2.47 – 2.39 (m, 2H), 2.31 (ddd, $J = 13.4, 8.2, 5.1$ Hz, 2H), 2.07 – 2.01 (m, 2H), 2.00 (s, 6H), 1.17 – 1.08 (m, 4H), 0.90 – 0.79 (m, 4H).
114 (TFA salt)	^1H NMR (500 MHz, DMSO- d_6) δ 10.36 (s, 2H), 8.62 (s, 2H), 7.82 (d, $J = 8.0$ Hz, 2H), 7.62 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 4.47 (d, $J = 7.1$ Hz, 2H), 4.35 – 4.20 (m, 4H), 3.65 – 3.55 (m, 4H), 2.35 – 2.28 (m, 2H), 2.00 (s, 6H), 1.95 – 1.80 (m, 4H), 1.16 (d, $J = 8.9$ Hz, 4H), 0.95 – 0.84 (m, 4H).
115	^1H NMR (500 MHz, DMSO- d_6) δ 10.33 (s, 2H), 8.51 (s, 2H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.59 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (d, $J = 7.5$ Hz, 2H), 4.12 (q, $J = 7.1$ Hz, 4H), 4.09 – 3.97 (m, 6H), 3.90 (d, $J = 13.9$ Hz, 2H), 3.61 (q, $J = 7.0, 6.4$ Hz, 2H), 2.83 (brs, 2H), 2.71 (dd, $J = 15.7, 6.3$ Hz, 2H), 2.60 (dd, $J = 15.7, 7.3$ Hz, 2H), 2.26 (td, $J = 8.4, 4.3$ Hz, 2H), 2.00 (s, 6H), 1.20 (t, $J = 7.1$ Hz, 6H), 1.14 (t, $J = 7.1$ Hz, 6H), 1.10 (d, $J = 8.5$ Hz, 4H), 0.89 – 0.79 (m, 4H).
116 (TFA salt)	^1H NMR (500 MHz, DMSO- d_6) δ 10.37 (s, 2H), 8.66 (s, 2H), 7.80 (d, $J = 8.0$ Hz, 2H), 7.64 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.00 (d, $J = 7.5$ Hz, 2H), 4.48 (d, $J = 10.8$ Hz, 2H), 4.40 (m, 2H), 4.15 (brs, 2H), 2.88 (brs, 4H), 2.40 – 2.27 (m, 2H), 1.99 (s, 6H), 1.17 (d, $J = 8.7$ Hz, 4H), 0.99 – 0.81 (m, 4H).
117	^1H NMR (500 MHz, DMSO- d_6) δ 10.32 (s, 2H), 8.51 (s, 2H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.59 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (dd, $J = 7.7, 1.3$ Hz, 2H), 4.12 (q, $J = 7.1$ Hz, 4H), 4.10 – 3.98 (m, 6H), 3.90 (d, $J = 13.9$ Hz, 2H), 3.61 (brs, 2H), 2.71 (dd, $J = 15.7, 6.3$ Hz, 2H), 2.60 (dd, $J = 15.7, 7.3$ Hz, 2H), 2.27 (ddd, $J = 11.0, 8.5, 5.3$ Hz, 2H), 2.00 (s, 6H), 1.20 (t, $J = 7.1$ Hz, 6H), 1.14 (t, $J = 7.1$ Hz, 6H), 1.15 – 1.07 (m, 4H), 0.89 – 0.78 (m, 4H).
118 (TFA salt)	^1H NMR (500 MHz, DMSO- d_6) δ 10.36 (s, 2H), 8.60 (s, 2H), 7.83 (d, $J = 8.0$ Hz, 2H), 7.61 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 7.4$ Hz, 2H), 4.31 (d, $J = 13.7$ Hz, 2H), 4.17 (d, $J = 13.7$ Hz, 2H), 3.83 (brs, 2H), 2.77 (dd, $J = 16.5, 6.3$ Hz, 2H), 2.67 (dd, $J = 16.5, 6.3$ Hz, 2H), 2.32 (tt, $J = 8.4, 4.9$ Hz, 2H), 2.00 (s, 6H), 1.19 – 1.09 (m, 4H), 0.93 – 0.83 (m, 4H).
119	^1H NMR (500 MHz, DMSO- d_6) δ 10.33 (s, 2H), 8.53 (s, 2H), 7.86 (d, $J = 7.9$ Hz, 2H), 7.59 (s, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 6.98 (d, $J = 7.5$ Hz, 2H), 4.22 (d, $J = 9.8$ Hz, 2H), 4.21 – 4.07 (m, 8H), 4.03 (d, $J = 6.2$ Hz, 4H), 3.07 (dt, $J = 9.8, 6.3$ Hz, 2H), 2.29 (td, $J = 8.3, 4.2$ Hz, 2H), 2.00 (s, 6H), 1.18 (t, $J = 7.1$ Hz, 12H), 1.16 – 1.08 (m, 4H), 0.85 (q, $J = 5.1$ Hz, 4H).
120 (Li salt)	^1H NMR (500 MHz, D $_2$ O) δ 8.51 (s, 2H), 7.58 (s, 2H), 7.44 (d, $J = 7.7$ Hz, 2H), 7.39 (t, $J = 7.7$ Hz, 2H), 7.22 (d, $J = 7.6$ Hz, 2H), 3.93 (s, 4H), 3.78 (s, 2H), 2.26 – 2.17 (m, 2H), 1.98 (s, 6H), 1.21 (q, $J = 5.9, 5.4$ Hz, 4H), 0.91 (q, $J = 5.4$ Hz, 4H).
121 (TFA salt)	^1H NMR (500 MHz, DMSO- d_6) δ 10.39 (s, 2H), 8.69 (s, 2H), 7.77 (dd, $J = 8.1, 1.3$ Hz, 2H), 7.64 (s, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.01 (dd, $J = 7.7, 1.3$ Hz, 2H), 4.49 (s, 4H), 4.23 (q, $J = 7.1$ Hz, 4H), 4.12 (s, 4H), 2.32 (td, $J = 8.4, 4.3$ Hz, 2H), 1.99 (s, 6H), 1.25 (t, $J = 7.1$ Hz, 6H), 1.23 – 1.16 (m, 4H), 0.94 (q, $J = 5.1$ Hz, 4H).

122 (TFA salt)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.39 (s, 2H), 8.70 (s, 2H), 7.76 (d, <i>J</i> = 7.9 Hz, 2H), 7.64 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.01 (d, <i>J</i> = 7.3 Hz, 2H), 4.51 (s, 4H), 4.03 (s, 4H), 2.38 – 2.28 (m, 2H), 1.99 (s, 6H), 1.23 – 1.11 (m, 4H), 0.98 – 0.87 (m, 4H).
123	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.31 (s, 2H), 8.53 (s, 2H), 7.88 (d, <i>J</i> = 8.0 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.7, 1.3 Hz, 2H), 4.10 (q, <i>J</i> = 7.0 Hz, 4H), 3.99 (dd, <i>J</i> = 14.0, 4.9 Hz, 2H), 3.87 (dd, <i>J</i> = 13.8, 5.8 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.30 (ddd, <i>J</i> = 10.8, 8.5, 5.2 Hz, 2H), 2.00 (s, 6H), 1.24 (d, <i>J</i> = 6.9 Hz, 6H), 1.20 (t, <i>J</i> = 7.1 Hz, 6H), 1.12 (d, <i>J</i> = 8.5 Hz, 4H), 0.91 – 0.78 (m, 4H).
124 (TFA salt)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.71 (s, 2H), 7.78 (d, <i>J</i> = 8.0 Hz, 2H), 7.66 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.01 (d, <i>J</i> = 7.5 Hz, 2H), 4.52 (s, 4H), 4.24 (q, <i>J</i> = 7.2 Hz, 2H), 2.33 (ddd, <i>J</i> = 13.5, 8.5, 5.4 Hz, 2H), 1.99 (s, 6H), 1.56 (d, <i>J</i> = 7.2 Hz, 6H), 1.23 – 1.15 (m, 4H), 1.01 – 0.86 (m, 4H).
125	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.51 (s, 2H), 7.86 (dd, <i>J</i> = 8.1, 1.3 Hz, 2H), 7.58 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.8, 1.4 Hz, 2H), 4.19 – 4.07 (m, 4H), 4.02 (d, <i>J</i> = 13.8 Hz, 2H), 3.80 (d, <i>J</i> = 13.8 Hz, 2H), 2.95 (brs, 2H), 2.30 (td, <i>J</i> = 8.3, 4.2 Hz, 2H), 2.00 (s, 6H), 1.86 (h, <i>J</i> = 6.7 Hz, 2H), 1.21 (t, <i>J</i> = 7.1 Hz, 6H), 1.12 (d, <i>J</i> = 9.0 Hz, 4H), 0.90 (d, <i>J</i> = 6.7 Hz, 6H), 0.87 (d, <i>J</i> = 6.8 Hz, 6H), 0.86 – 0.82 (m, 4H).
126 (TFA salt)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.69 (s, 2H), 7.80 (d, <i>J</i> = 8.1 Hz, 2H), 7.64 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.00 (d, <i>J</i> = 7.5 Hz, 2H), 4.40 (s, 4H), 2.38 – 2.24 (m, 4H), 2.00 (s, 6H), 1.17 (d, <i>J</i> = 8.2 Hz, 4H), 1.06 (d, <i>J</i> = 6.9 Hz, 6H), 0.96 (d, <i>J</i> = 6.8 Hz, 6H), 0.96 – 0.88 (m, 4H).
127	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.31 (s, 2H), 8.50 (s, 2H), 7.88 (d, <i>J</i> = 8.0 Hz, 2H), 7.57 (s, 2H), 7.31 (t, <i>J</i> = 7.8 Hz, 2H), 6.97 (d, <i>J</i> = 7.1 Hz, 2H), 4.08 (q, <i>J</i> = 7.1 Hz, 4H), 4.07 (s, 4H), 2.37 – 2.29 (m, 2H), 1.99 (s, 6H), 1.19 (t, <i>J</i> = 7.1 Hz, 6H), 1.18 – 1.16 (m, 4H), 1.16 – 1.09 (m, 4H), 0.99 (q, <i>J</i> = 3.8 Hz, 4H), 0.89 – 0.81 (m, 4H).
128 (TFA salt)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.35 (s, 2H), 8.61 (s, 2H), 7.83 (d, <i>J</i> = 8.0 Hz, 2H), 7.61 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.99 (d, <i>J</i> = 7.3 Hz, 2H), 4.41 (brs, 4H), 2.39 – 2.30 (m, 2H), 1.99 (s, 6H), 1.43 – 1.26 (m, 8H), 1.18 (d, <i>J</i> = 7.9 Hz, 4H), 0.91 (brs, 4H).
129	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.49 (s, 2H), 7.86 (d, <i>J</i> = 8.0 Hz, 2H), 7.58 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.10 (q, <i>J</i> = 7.1 Hz, 4H), 3.89 (s, 4H), 3.37 (s, 4H), 2.44 (tt, <i>J</i> = 8.4, 5.3 Hz, 2H), 2.31 (s, 6H), 2.00 (s, 6H), 1.20 (t, <i>J</i> = 7.1 Hz, 6H), 1.17 – 1.11 (m, 4H), 0.89 – 0.81 (m, 4H).
130 (TFA salt)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 2H), 8.68 (s, 2H), 7.79 (d, <i>J</i> = 8.0 Hz, 2H), 7.62 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.01 (d, <i>J</i> = 7.5 Hz, 2H), 4.50 (s, 4H), 3.99 (s, 4H), 2.73 (s, 6H), 2.43 (ddd, <i>J</i> = 13.4, 8.6, 5.2 Hz, 2H), 2.00 (s, 6H), 1.21 (brd, <i>J</i> = 8.1 Hz, 4H), 0.95 (brd, <i>J</i> = 4.4 Hz, 4H).
131	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.52 (s, 2H), 7.88 (d, <i>J</i> = 8.1 Hz, 2H), 7.58 (s, 2H), 7.32 (t, <i>J</i> = 7.9 Hz, 3H), 6.98 (d, <i>J</i> = 7.7 Hz, 2H), 3.87 (d, <i>J</i> = 13.4 Hz, 2H), 3.83 (d, <i>J</i> = 13.4 Hz, 2H), 3.60 (s, 6H), 3.11 – 3.01 (m, 2H), 2.78 (t, <i>J</i> = 8.7 Hz, 2H), 2.70 (dd, <i>J</i> = 9.2, 6.3 Hz, 2H), 2.58 (t, <i>J</i> = 7.0 Hz, 4H), 2.38 – 2.29 (m, 2H), 2.06 – 1.93 (m, 4H), 2.00 (s, 6H),

	1.16 – 1.09 (m, 4H), 0.89 – 0.82 (m, 4H).
132	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.52 (s, 2H), 7.87 (dd, <i>J</i> = 8.0, 3.7 Hz, 2H), 7.58 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 2H), 3.83 (q, <i>J</i> = 13.6 Hz, 4H), 2.95 – 2.83 (m, 2H), 2.79 – 2.71 (m, 2H), 2.69 (t, <i>J</i> = 7.7 Hz, 2H), 2.57 (q, <i>J</i> = 7.8 Hz, 4H), 2.39 – 2.29 (m, 2H), 2.00 (s, 6H), 2.00 – 1.89 (m, 4H), 1.17 – 1.09 (m, 4H), 0.90 – 0.80 (m, 4H).
134 (TFA salt)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.39 (s, 2H), 8.75 (s, 2H), 7.77 (d, <i>J</i> = 8.1 Hz, 2H), 7.62 (s, 2H), 7.33 (t, <i>J</i> = 7.8 Hz, 2H), 7.01 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.76 (brs, 4H), 3.76 (brs, 4H), 3.62 – 3.40 (m, 6H), 2.43 – 2.35 (m, 2H), 2.26 (brs, 2H), 1.99 (s, 6H), 1.23 (d, <i>J</i> = 8.3 Hz, 4H), 1.02 – 0.91 (m, 4H).
136	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.57 (s, 2H), 7.89 (d, <i>J</i> = 8.3 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.9 Hz, 2H), 6.98 (d, <i>J</i> = 7.7 Hz, 2H), 3.98 (s, 4H), 3.94 – 3.89 (m, 2H), 2.62 – 2.53 (m, 2H), 2.34 (dd, <i>J</i> = 14.8, 4.9 Hz, 2H), 2.31 – 2.23 (m, 2H), 2.23 – 2.14 (m, 2H), 2.01 (s, 6H), 1.12 (brd, <i>J</i> = 8.6 Hz, 4H), 0.85 (brd, <i>J</i> = 5.2 Hz, 4H).
137	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 2H), 8.57 (s, 2H), 7.88 (d, <i>J</i> = 7.9 Hz, 2H), 7.69 (s, 2H), 7.59 (s, 2H), 7.31 (t, <i>J</i> = 7.8 Hz, 2H), 6.97 (d, <i>J</i> = 7.5 Hz, 2H), 3.99 (d, <i>J</i> = 14.1 Hz, 2H), 3.95 (d, <i>J</i> = 14.2 Hz, 2H), 3.69 – 3.59 (m, 2H), 2.58 (d, <i>J</i> = 6.0 Hz, 4H), 2.28 (ddd, <i>J</i> = 13.6, 8.4, 5.2 Hz, 2H), 2.15 – 2.03 (m, 6H), 2.00 (s, 6H), 1.75 – 1.63 (m, 2H), 1.17 – 1.09 (m, 4H), 0.87 – 0.81 (m, 4H).
138	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.57 (s, 2H), 7.88 (d, <i>J</i> = 8.0 Hz, 2H), 7.59 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (d, <i>J</i> = 7.3 Hz, 2H), 4.52 (dt, <i>J</i> = 47.7, 5.0 Hz, 4H), 4.00 (s, 4H), 2.87 (dt, <i>J</i> = 27.6, 5.0 Hz, 4H), 2.32 – 2.25 (m, 2H), 2.00 (s, 6H), 1.18 – 1.08 (m, 4H), 0.88 – 0.82 (m, 4H).
139	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.57 (s, 2H), 7.87 (dd, <i>J</i> = 8.1, 1.3 Hz, 2H), 7.60 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 6.07 (tt, <i>J</i> = 56.3, 4.2 Hz, 2H), 4.03 (s, 4H), 2.96 (td, <i>J</i> = 15.9, 4.3 Hz, 4H), 2.27 (tt, <i>J</i> = 8.3, 5.2 Hz, 2H), 2.00 (s, 6H), 1.16 – 1.09 (m, 4H), 0.89 – 0.81 (m, 4H).
140	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 2H), 8.56 (s, 2H), 7.87 (dd, <i>J</i> = 8.1, 1.3 Hz, 2H), 7.61 (s, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 6.98 (dd, <i>J</i> = 7.6, 1.3 Hz, 2H), 4.07 (d, <i>J</i> = 6.0 Hz, 4H), 3.05 – 2.97 (m, 2H), 2.26 (tt, <i>J</i> = 8.4, 5.2 Hz, 2H), 2.00 (s, 6H), 1.17 – 1.09 (m, 4H), 0.90 – 0.81 (m, 4H).
141	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.81 (s, 1H), 10.39 (s, 1H), 8.56 – 8.49 (m, 3H), 7.96 (d, <i>J</i> = 8.0 Hz, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.53 (t, <i>J</i> = 7.9 Hz, 1H), 7.36 (t, <i>J</i> = 7.8 Hz, 1H), 7.13 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.05 (d, <i>J</i> = 7.7 Hz, 1H), 4.48 (s, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.78 (s, 4H), 3.47 (d, <i>J</i> = 5.0 Hz, 4H), 2.58 (t, <i>J</i> = 5.7 Hz, 4H), 2.06 (s, 3H).
Positive compound	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 8.58 (s, 1H), 7.98 (s, 1H), 7.86 (dd, <i>J</i> = 8.0, 1.3 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.42 – 7.36 (m, 1H), 7.36 – 7.28 (m, 3H), 7.08 (dd, <i>J</i> = 7.6, 1.3 Hz, 1H), 4.51 (t, <i>J</i> = 5.4 Hz, 1H), 3.83 (s, 2H), 3.49 (q, <i>J</i> = 5.7 Hz, 2H), 2.62 (t, <i>J</i> = 5.8 Hz, 2H), 2.45 (s, 3H), 2.18 (s, 3H).

Biological Test Evaluation

A. PD1-PDL1 HTRF Binding Activity Test

The effect of compounds and positive compounds of the examples of the present invention on the interaction between PD-1 and PD-L1 was determined by the PD-1/PD-L1 binding assay kit from Cisbio (#64ICP01PEG or 64ICP01PEH). The detailed experimental process was as follows:

1. Pre-diluted compound solution, 4 μ L of Tag1-PD-L1 and 4 μ L of Tag2-PD1 were added to each well of a 384-well plate;

2. After the mixture was incubated at room temperature for 15 min, 5 μ L of anti-Tag1-Eu3+ antibody and 5 μ L of anti-Tag2-XL665 antibody were then added;

3. After incubated for 2 hrs at room temperature or overnight at 4 °C, plates were read on Envision of Pelkin Elmer; and readings at 665 nm and 620 nm were recorded, and the ratio of the two readings was taken as a reading for each well;

4. The reading of each well after compound treatment was compared with the reading of DMSO treated wells to obtain the percent inhibition of the compound; and

5. IC₅₀ values of compounds and positive compounds of the examples of the present invention were determined by non-linear regression analysis of percent inhibition at different compound concentrations. The specific experimental results were shown in Table 1.

B. Jurkat Reporter Gene Cellular Assay

The effect of compounds of the examples of the present invention and positive compounds on the interaction between PD-1 and PD-L1 expressed on cell surfaces, and the related influence on T cell functions, were determined by a Jurkat reporter gene cellular assay.

Briefly, the reporter gene plasmid of NF- κ B-luc and the plasmid of human PD-1 were transfected into Jurkat cells to establish a stably transfected cell line capable of stably expressing both PD-1 and NF- κ B-Luc reporter genes; the expression level of PD-1 on the cell surface was confirmed by flow cytometry; and the expression of the reporter gene was confirmed via the response of the reporter gene stimulated by OKT-3 and Raji cells.

In addition, the plasmid of human PD-L1 was transfected into Raji cells to obtain a cell line capable of stably expressing PD-L1. Jurkat/NF- κ B-luc/PD1 cells and Raji-PD-L1 cells were then cocultured and stimulated with OKT-3. On this basis, the compounds were added, and the enhancement of the signal pathway of T cell activation by the inhibitory effect of the compounds on the interaction between PD-1 and PD-L1 was evaluated by readings of reporter gene responses. The specific experimental process was as follows:

1. 30 μ L of compound or antibody solution was added to each well of a white 96-well plate (corning, 3610) at different diluted concentrations, and 10 μ L of OKT3 (Biolegend, 317326) was then added (the final concentration of OKT3: 1 μ g/mL);

2. 20 μ L of Raji-PD-L1 cell suspension was added to each well with 5×10^4 cells for each well, and was incubated in an incubator for 20 min;

3. 20 μ L of Jurkat/NF- κ b-luc/PD-1 cell suspension was added to each well with 5×10^4 cells for each well, and well mixed, and 6 hrs later, Bright-glo (Promega, E2620) was applied and plates were read on Envision;

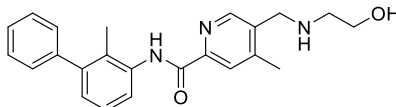
4. the reading of each well treated with the compound was compared with the reading of each well treated with DMSO to obtain the activation fold of the compound; and

5. EC₅₀ values of compounds and positive compounds of the examples of the present invention were determined by non-linear regression analysis of activation folds at different compound concentrations. The specific experimental results were shown in Table 1:

Table 1: Biological Test Results

Example No.	PD1-PDL1 HTRF Binding Activity IC ₅₀ /nM	Cell Activity EC ₅₀ /nM	Example No.	PD1-PDL1 HTRF Binding Activity IC ₅₀ /nM	Cell Activity EC ₅₀ /nM
1	0.17	137	72	0.48	1563
2	0.18	109	73	0.29	812
3	0.20	37	74	0.14	303
4	0.064	1336	75	0.36	782
5	0.36	64	76	7.80	3064
6	0.79	658	77	0.41	297
7	0.096	139	78	10.9	2913
8	0.41	186	79	0.65	171
9	3.8	> 10000	80	0.082	3742
10	0.28	50	81	0.43	900
11	0.60	134	82	1.90	566
12	1.9	594	83	1.04	309
13	0.13	109	84	1.36	603
14	227	NT	85	0.45	341
15	0.83	511	86	1.34	406
16	0.14	310	87	1.08	800
17	1.5	> 10000	88	0.41	182
18	0.34	209	89	0.87	427
19	0.15	86	90	0.36	131
20	0.36	4216	91	0.16	39
21	0.66	83	92	0.87	54.7
22	0.28	5170	93	1.49	104
23	0.31	249	94	4.75	566
24	3.20	1047	95	2.02	125
25	0.37	124	96	1.44	87
26	65.3	NT	97	3.38	221
27	0.28	128	98	3.78	241

28	9.55	> 10000	99	1.43	260
29	0.36	1464	100	1.51	121.7
30	1.24	448	101	1.09	267
31	1.0	2083	102	3.61	194
32	0.27	53	103	4.11	206
33	0.65	109	104	1.57	296
34	0.21	111	105	0.27	14.1
35	1.11	257	106	22.5	1263
36	0.74	456	107	15.2	752.9
37	0.040	118	108 (TFA salt)	0.84	42.3
38	0.83	6998	109	375	> 10000
39	0.86	225	110 (TFA salt)	0.67	51
40	0.29	172	111	79.4	5948
41	0.032	74	112 (TFA salt)	1.02	34.6
42	0.28	60	113	6.77	979
43	0.29	11	114 (TFA salt)	5.2	89
44	0.24	55	115	> 400	> 10000
45	0.22	41	116 (TFA salt)	0.94	1340
46	0.25	64	117	> 400	> 10000
47	0.27	46	118 (TFA salt)	1.17	1042
48	0.31	102	119	> 400	> 10000
49	0.33	104	120 (Li salt)	1.43	1761
50	0.33	229	121 (TFA salt)	16.6	1341
51	0.22	288	122 (TFA salt)	1.14	19
52	0.40	508	123	22.0	2409
53	0.15	52	124 (TFA salt)	1.09	14.7
54	0.21	4768	125	> 2000	> 10000
55	0.40	82	126	1.11	64

			(TFA salt)		
56	0.64	172	127	112.7	> 10000
57	0.36	> 10000	128 (TFA salt)	1.32	77.8
58	0.22	625	129	101.5	> 10000
59	0.31	70	130 (TFA salt)	0.99	600
60	0.034	580	131	21.8	2579
61	0.18	319	132	0.20	23.1
62	0.25	639	133	11.8	1899
63	0.25	4600	134 (TFA salt)	0.82	21.0
64	10.7	1862	136	0.32	27.4
65	0.12	132	137	2.07	108
66	0.64	691	138	5.03	581
67	0.51	349	139	119.7	> 10000
68	0.31	261	140	15.1	2711
69	0.39	105	141	0.75	74
70	0.54	2200	Positive compound	2.4	> 10000
71	0.33	756			
Notes	1, "NT" is an abbreviation of "Not Tested", and means that an object has not been detected yet. 2. The positive compound is the compound of example 33 of patent WO2017106634, and has a chemical structure shown as follows: 				

The bioactivity data of the compounds of the specific examples indicates that the series of compounds of the present invention have a strong inhibitory effect on the interaction between PD-1 and PD-L1, and moreover, such an inhibitory effect can enhance or recover the activation of T cells at the cellular level.

5 C. Pharmacokinetic Assay in Mice

1. Purpose of study

The purpose of this study was to study the pharmacokinetic behaviors of some compounds of the present invention, and administration routes were: per oral administration (PO) to ICR mice:

- 10 1). 10 mg/kg: examples 1, 3, 5, 8, 46, 104 and 141.
- 2). 30 mg/kg: examples 4, 26 and 64.

2. Testing scheme

2.1 Tested medicaments

The compounds used in this test came from the compounds of the specific examples of the present invention.

2.2 Tested animal

ICR mice male N = 3 original source: Shanghai Sippr-BK Laboratory Animal Co. Ltd.

2.3 Preparation and administration of medicaments

The compounds were weighed, and dissolved in a solvent of 0.5% SDS + 0.5% CMCNa. The mixture solutions were mixed well by shaking and ultrasonic treatment to obtain colorless clear solutions. The solutions were orally administered to nine mice after an overnight fast. The dosage of administration was 10 mg/kg (or 30 mg/kg).

2.4 Sampling

With about 90 μ L/time point, blood was drawn from the submaxillary vein, and heparin sodium was added for anticoagulation. The blood samples were placed onto the ice, and were centrifuged (centrifugation conditions: 8000 r/min, 6 min, 2-8 $^{\circ}$ C) within 1 hr to obtain plasmas. The time points for blood sampling were at 0 hr, 0.25 hr, 0.5 hr, 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs and 24 hrs after administration. The samples were stored in a refrigerator at -20 $^{\circ}$ C.

40 μ L of plasma sample was added to 160 μ L of cold acetonitrile containing an internal standard, and the mixture solution was vortexed for 3 min and centrifuged at 11,000 r/min for 5 min. 100 μ L of supernate was taken and added to 100 μ L of water, and 5 μ L of the sample was taken and analyzed by LC/MS/MS. Only the original compounds were analyzed for examples 1, 3, 5, 8, 46 and 141 (for results, see table 2); and both the original compounds and possible products of ester hydrolysis, namely example 2, 27, 65 and 105, were analyzed for examples 4, 26, 64 and 104 (for results, see table 3).

2.5 Test results

Table 2: PK Results for Per Oral Administration (PO) of 10 mg/kg of Compounds to Mice

Compound No.	C _{max} (ng/mL)	T _{max} (h)	AUC _{last} (hr * ng/mL)	T _{1/2} (h)	MRT (h)
1	*	1	+	2.4	3.3
3	**	0.5	+++	12.9	16.7
5	**	2	1685	8.3	10.2
8	319	2	++	3	5.4
46	*	4	++	10.7	15.5
141	BQL	NA	NA	NA	NA

Table 3: PK Results for Per Oral Administration (PO) of Compounds to Mice

Compound	Tested	C _{max}	T _{max}	AUC _{last} (hr	T _{1/2} (h)	MRT (h)
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No.	Compound	(ng/mL)	(h)	* ng/mL)		
4	4	BQL	NA	NA	NA	NA
	2	6480	0.5	8901	1.6	1.6
26	26	***	6	+++	3.6	7
	27	BQL	NA	NA	NA	NA
64	64	***	2	+++	3.7	4.6
	65	BQL	NA	NA	NA	NA
104*	104	BQL	NA	NA	NA	NA
	105	1813	0.5	3968	20	17

Notes: The dosage of administration of example 104* is 10 mpk. In Table 2 and Table 3:

1. "BQL" means that it is below the detection limit of the instrument. "NA" means it is ineffective or none.

5 2. "+++" means $AUC_{last} (hr * ng/mL) > 2,000$; "++" means $500 < AUC_{last} (hr * ng/mL) \leq 2,000$; "+" means $AUC_{last} (hr * ng/mL) \leq 500$.

3. "****" means $C_{max} (ng/mL) > 500$; "***" means $100 < C_{max} (ng/mL) \leq 500$;

"**" means $C_{max} (ng/mL) \leq 100$.

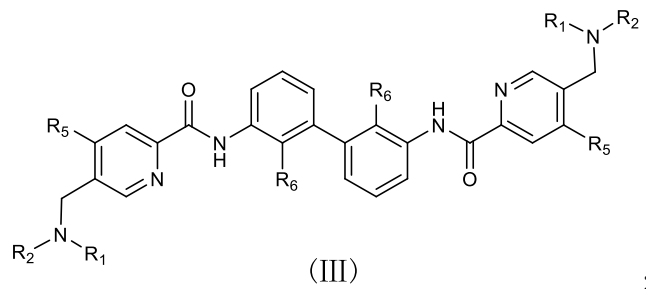
10 Example 4 and example 104 were absorbed into the bodies of the mice by oral administration, and rapidly became corresponding acids (example 2 and example 105) via ester hydrolysis. Compared with example 2, the in-vivo metabolism of example 105 significantly slowed down, and the half-life period was prolonged to 20 hrs from 1.6 hrs. The methyl piperidine-2-carboxylate compounds (example 26 and example 64) were orally administered to the mice, and existed almost only as the original forms in their
15 bodies, and no product of ester hydrolysis was detected.

All documents mentioned in the present invention are incorporated by reference, just as each document is cited separately as a reference. In addition, it should be understood that various modifications or changes may be made by those skilled in the art after reading the above teachings of the present invention, and these equivalent forms also fall within
20 the scope defined by the claims appended hereto.

CLAIMS

We claim:

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



wherein, R₆ is methyl;

R₅ is selected from the group consisting of hydrogen, deuterium, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl and methoxy;

R₁ and R₂ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl C₁₋₈ alkyl, 3-10 membered heterocyclyl, 3-10 membered heterocyclyl C₁₋₈ alkyl, C₅₋₁₀ aryl, C₅₋₁₀ aryl C₁₋₈ alkyl and 5-10 membered heteroaryl, or, R₁ and R₂, together with the nitrogen atom directly attached thereto, form 3-10 membered heterocyclyl, wherein the above-mentioned groups of R₁ and R₂ are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, =O, -C₀₋₈ alkyl-S(O)(=N-R₇)R₉, -C₀₋₈ alkyl-N=S(O)R₉R₁₀, -C₀₋₈ alkyl-N=SR₉R₁₀, -C₀₋₈ alkyl-P(O)(OH)R₁₂, -C₀₋₈ alkyl-SF₅, -C₀₋₈ alkyl-O-S(O)₂R₁₂, -C₀₋₈ alkyl-S(O)_rR₁₂, -C₀₋₈ alkyl-O-R₁₃, -C₀₋₈ alkyl-C(O)OR₁₃, -C₀₋₈ alkyl-C(O)R₁₄, -C₀₋₈ alkyl-O-C(O)R₁₄, -C₀₋₈ alkyl-NR₁₅R₁₆, -C₀₋₈ alkyl-C(=NR₁₅)R₁₄, -C₀₋₈ alkyl-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈ alkyl-C(O)NR₁₅R₁₆ and -C₀₋₈ alkyl-N(R₁₅)-C(O)R₁₄;

R₇ is selected from the group consisting of hydrogen, deuterium, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈alkyl-S(O)_rR₁₂, -C₀₋₈ alkyl-C(O)OR₁₃, -C₀₋₈ alkyl-C(O)R₁₄ and -C₀₋₈ alkyl-C(O)NR₁₅R₁₆, wherein R₇ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈ alkyl-S(O)_rR₁₂, -C₀₋₈ alkyl-O-R₁₃, -C₀₋₈ alkyl-C(O)OR₁₃, -C₀₋₈ alkyl-C(O)R₁₄, -C₀₋₈ alkyl-O-C(O)R₁₄, -C₀₋₈ alkyl-NR₁₅R₁₆, -C₀₋₈ alkyl-C(=NR₁₅)R₁₄, -C₀₋₈ alkyl-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈ alkyl-C(O)NR₁₅R₁₆ and -C₀₋₈ alkyl-N(R₁₅)-C(O)R₁₄;

R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl and 5-10 membered heteroaryl, or, R₉ and R₁₀, together with the sulfur atom directly attached thereto, form 3-10 membered heterocyclyl, wherein the above-mentioned groups of R₉ and R₁₀ are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, cyano, nitro, azido, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, -C₀₋₈ alkyl-S(O)_rR₁₂, -C₀₋₈ alkyl-O-R₁₃, -C₀₋₈ alkyl-C(O)OR₁₃, -C₀₋₈ alkyl-C(O)R₁₄, -C₀₋₈ alkyl-O-C(O)R₁₄, -C₀₋₈ alkyl-NR₁₅R₁₆, -C₀₋₈ alkyl-C(=NR₁₅)R₁₄, -C₀₋₈ alkyl-N(R₁₅)-C(=NR₁₆)R₁₄, -C₀₋₈ alkyl-C(O)NR₁₅R₁₆ and -C₀₋₈ alkyl-N(R₁₅)-C(O)R₁₄;

each R₁₂ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, halogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocycliloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₅R₁₆, wherein each R₁₂ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, carbonyl, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocycliloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₅R₁₆;

each R₁₃ is independently selected from the group consisting of hydrogen, deuterium, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl and 5-10 membered heteroaryl, wherein each R₁₃ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, carbonyl, cyano, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocycliloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₅R₁₆;

each R₁₄ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocycliloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₅R₁₆, wherein each R₁₄ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, cyano, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, 3-10 membered heterocyclyl, 3-10 membered heterocycliloxy, C₅₋₁₀ aryl, C₅₋₁₀ aryloxy, 5-10 membered heteroaryl, 5-10 membered heteroaryloxy and -NR₁₅R₁₆;

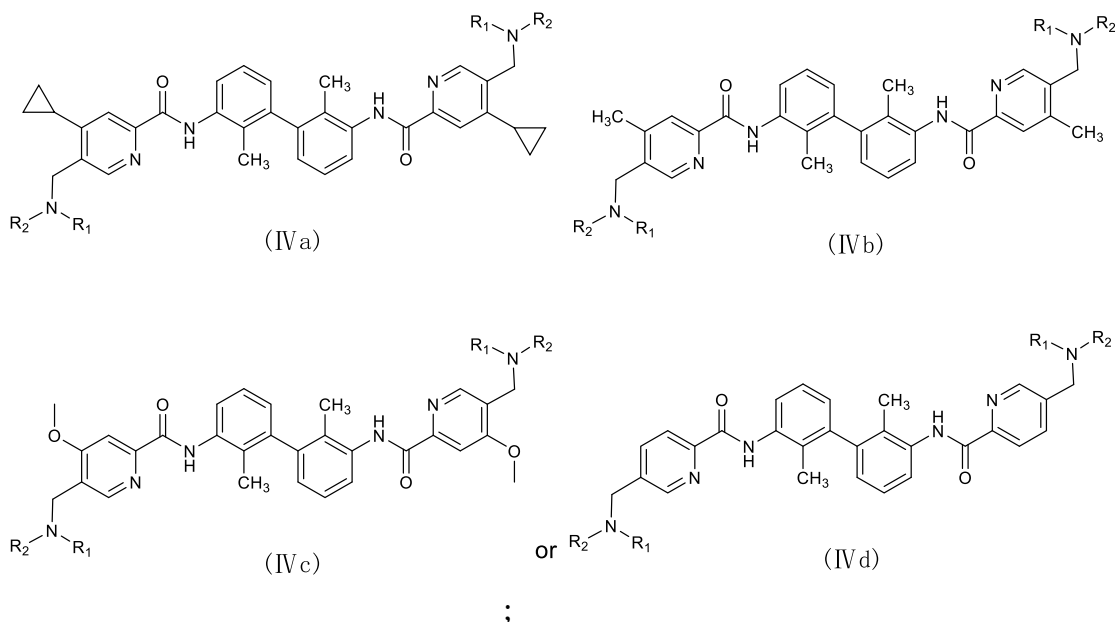
R₁₅ and R₁₆ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₁₀ alkoxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, 3-10 membered heterocyclyl, C₅₋₁₀ aryl, 5-10 membered heteroaryl, sulfinyl, sulfonyl, methanesulfonyl, isopropylsulfonyl, cyclopropylsulfonyl, *p*-toluenesulfonyl,

aminosulfonyl, dimethylaminosulfonyl, amino, monoalkylamino, dialkylamino and C₁₋₁₀ alkanoyl, wherein the above-mentioned groups of R₁₅ and R₁₆ are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₁₋₁₀ 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 C₁₋₁₀ alkanoyl; or,

R₁₅ and R₁₆, together with the nitrogen atom directly attached thereto, form 4-10 membered heterocyclyl or 4-10 membered heteroaryl, the 4-10 membered heterocyclyl or 4-10 membered heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ deuterioalkyl, C₁₋₁₀ 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 C₁₋₁₀ alkanoyl;

each r is 0, 1 or 2.

2. The compound of formula (III), the stereoisomer or pharmaceutically acceptable salt thereof of claim 1, wherein, the compound of formula (III) is a compound with the structure shown as formula (IV a), (IV b), (IV c) or (IV d):



wherein, R₁ and R₂ are each independently defined as in claim 1.

3. The compound of formula (III), the stereoisomer or pharmaceutically acceptable salt thereof of claim 1 or 2, wherein, R₁ and R₂ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl,

C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl and 5-8 membered heteroaryl, or, R₁ and R₂, together with the nitrogen atom directly attached thereto, form 3-8 membered heterocyclyl, the heteroatom in the heterocyclyl is selected from the group consisting of N, O, S and/or Si, wherein the above-mentioned groups of R₁ and R₂ 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, C₁₋₄ deuterioalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, =O, -S(O)(=N-R₇)R₉, -N=S(O)R₉R₁₀, -N=SR₉R₁₀, -P(O)(OH)R₁₂, -SF₅, -O-S(O)₂R₁₂, -S(O)_rR₁₂, -O-R₁₃, -C(O)OR₁₃, -C(O)R₁₄, -O-C(O)R₁₄, -NR₁₅R₁₆, -C(=NR₁₅)R₁₄, -N(R₁₅)-C(=NR₁₆)R₁₄, -C(O)NR₁₅R₁₆ and -N(R₁₅)-C(O)R₁₄; and

R₇, R₉, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆ and r are defined as in claim 1.

4. The compound of formula (III), the stereoisomer or pharmaceutically acceptable salt thereof of claim 3, wherein, R₁ is hydrogen, deuterium or methyl; R₂ is selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl and 5-8 membered heteroaryl, or, R₁ and R₂, together with the nitrogen atom directly attached thereto, form 3-8 membered heterocyclyl, the heteroatom in the heterocyclyl is selected from the group consisting of N, O, S and/or Si, wherein the above-mentioned groups of R₁ and R₂ 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, C₁₋₄ deuterioalkyl, C₃₋₈ cycloalkyl, 3-8 membered heterocyclyl, C₅₋₈ aryl, 5-8 membered heteroaryl, =O, -S(O)(=N-R₇)R₉, -N=S(O)R₉R₁₀, -N=SR₉R₁₀, -P(O)(OH)R₁₂, -SF₅, -O-S(O)₂R₁₂, -S(O)_rR₁₂, -O-R₁₃, -C(O)OR₁₃, -C(O)R₁₄, -O-C(O)R₁₄, -NR₁₅R₁₆, -C(=NR₁₅)R₁₄, -N(R₁₅)-C(=NR₁₆)R₁₄, -C(O)NR₁₅R₁₆ and -N(R₁₅)-C(O)R₁₄;

R₇ is selected from the group consisting of hydrogen, deuterium, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl, methanesulfonyl and acetyl, wherein R₇ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, hydroxy, methyl, ethyl, trifluoromethyl, difluoromethyl, trideuteriomethyl, dideuteriomethyl, cyclopropyl, phenyl, diazole, triazole, methoxy, ethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, acetyl, acetoxyl, amino and dimethylamino;

R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl and 5-8 membered heteroaryl, or, R₉ and R₁₀, together with the sulfur atom directly attached thereto, form 3-6 membered heterocyclyl, wherein the above-mentioned groups of R₉ and R₁₀ are optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, cyano, hydroxy, methyl, ethyl, trifluoromethyl, difluoromethyl, trideuteriomethyl, dideuteriomethyl, cyclopropyl,

phenyl, diazole, triazole, methoxy, ethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, acetyl, acetoxy, amino and dimethylamino;

each R₁₂ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, halogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl and -NR₁₅R₁₆, wherein each R₁₂ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, fluorine, chlorine, hydroxy, carbonyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl, amino and dimethylamino;

each R₁₃ is independently selected from the group consisting of hydrogen, deuterium, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl and 5-8 membered heteroaryl, wherein each R₁₃ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, carbonyl, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocycliloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy and -NR₁₅R₁₆;

each R₁₄ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocycliloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy and -NR₁₅R₁₆, wherein each R₁₄ is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocycliloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy and -NR₁₅R₁₆;

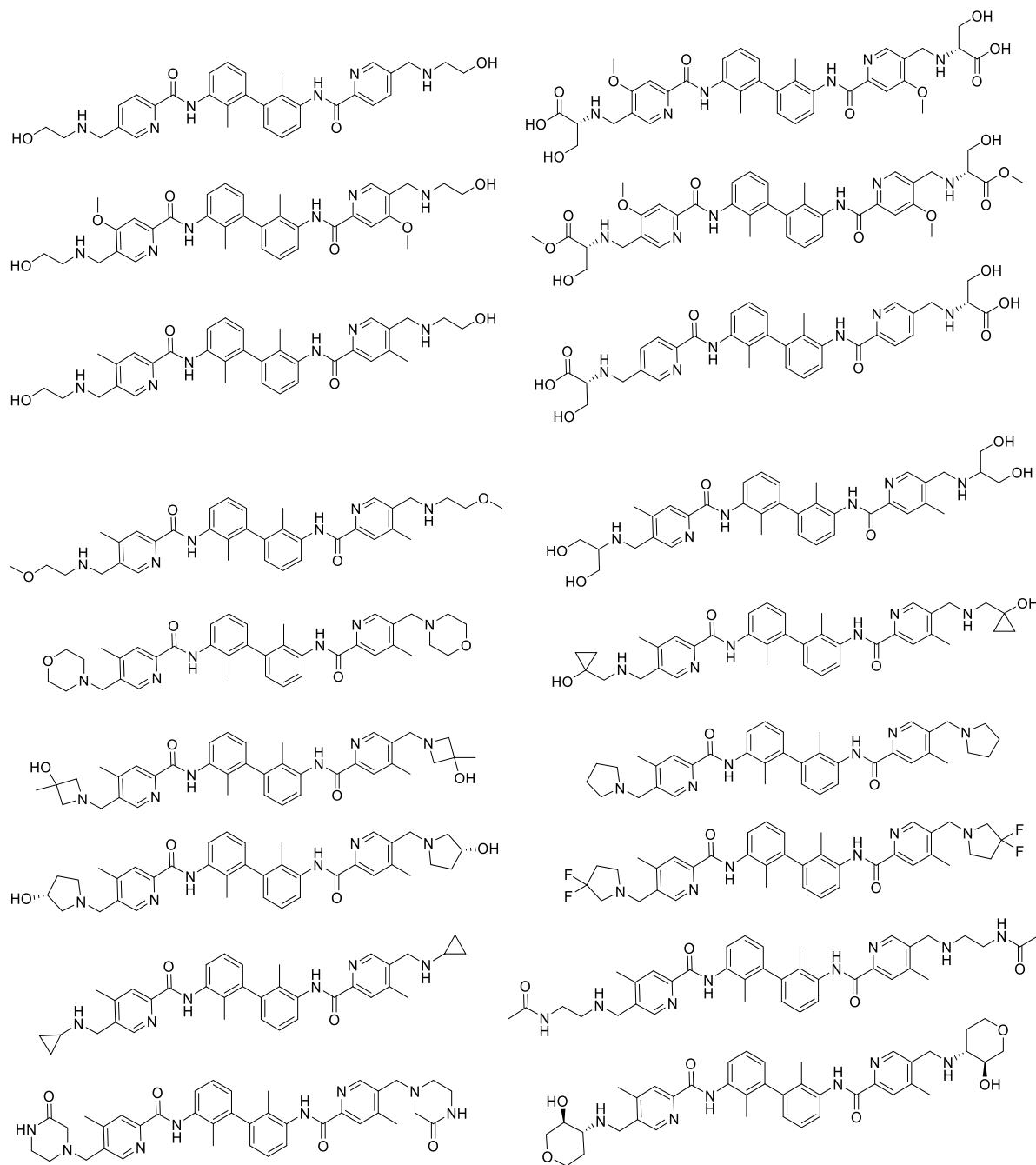
each of R₁₅ and R₁₆ is independently selected from the group consisting of hydrogen, deuterium, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-8 membered heteroaryl, sulfinyl, sulfonyl, methanesulfonyl, isopropylsulfonyl, cyclopropylsulfonyl, *p*-toluenesulfonyl, aminosulfonyl, dimethylaminosulfonyl, amino, monoalkylamino, dialkylamino and C₁₋₄ alkanoyl, wherein the above-mentioned groups of R₁₅ and R₁₆ are optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocycliloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy, amino, monoalkylamino, dialkylamino and C₁₋₄ alkanoyl; or,

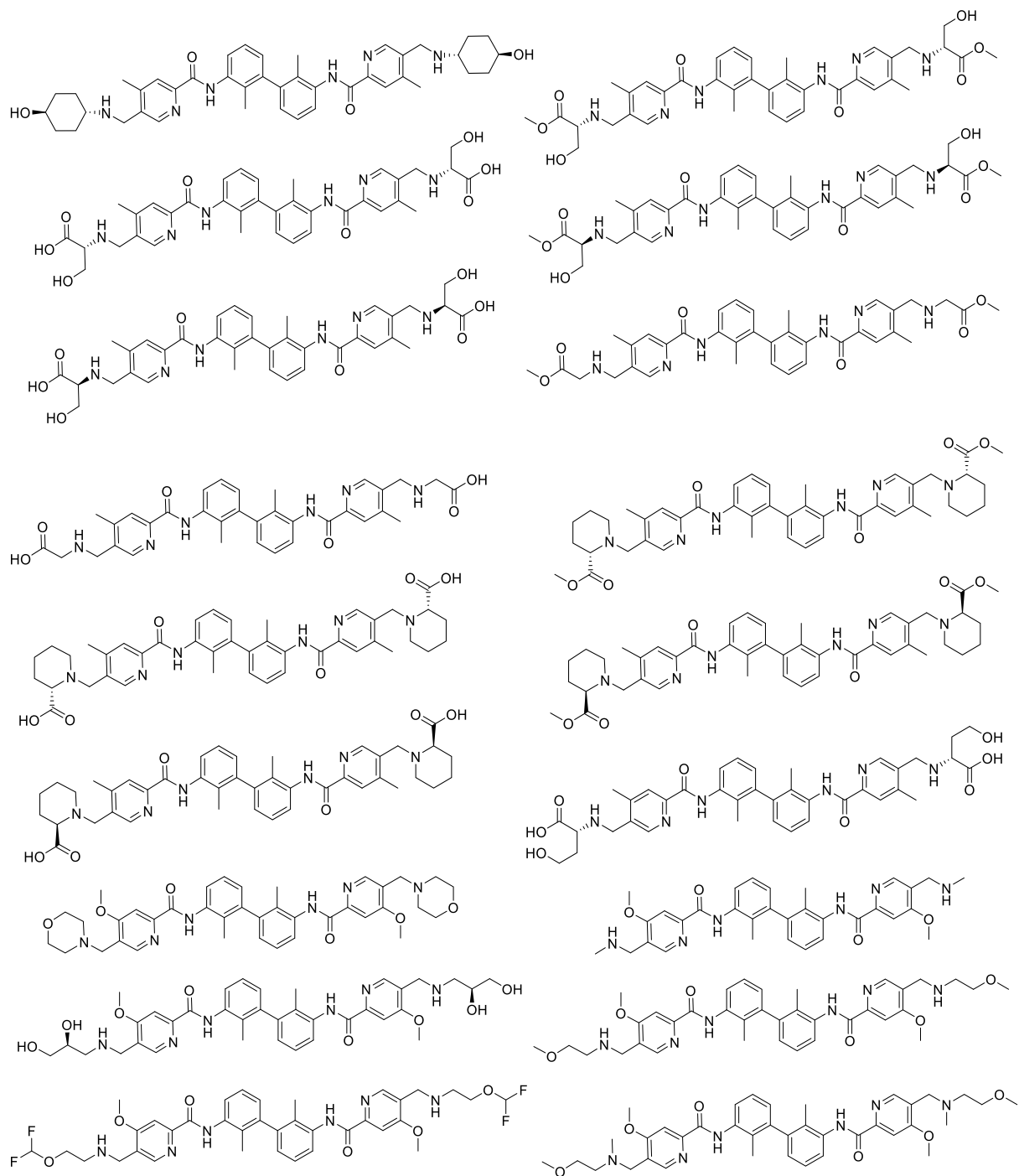
R₁₅ and R₁₆, together with the nitrogen atom directly attached thereto, form 4-6 membered heterocyclyl or 4-6 membered heteroaryl, the 4-6 membered heterocyclyl or 4-6 membered heteroaryl is optionally further substituted by one or more substituents selected from the group consisting of deuterium, halogen, hydroxy, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ deuterioalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆

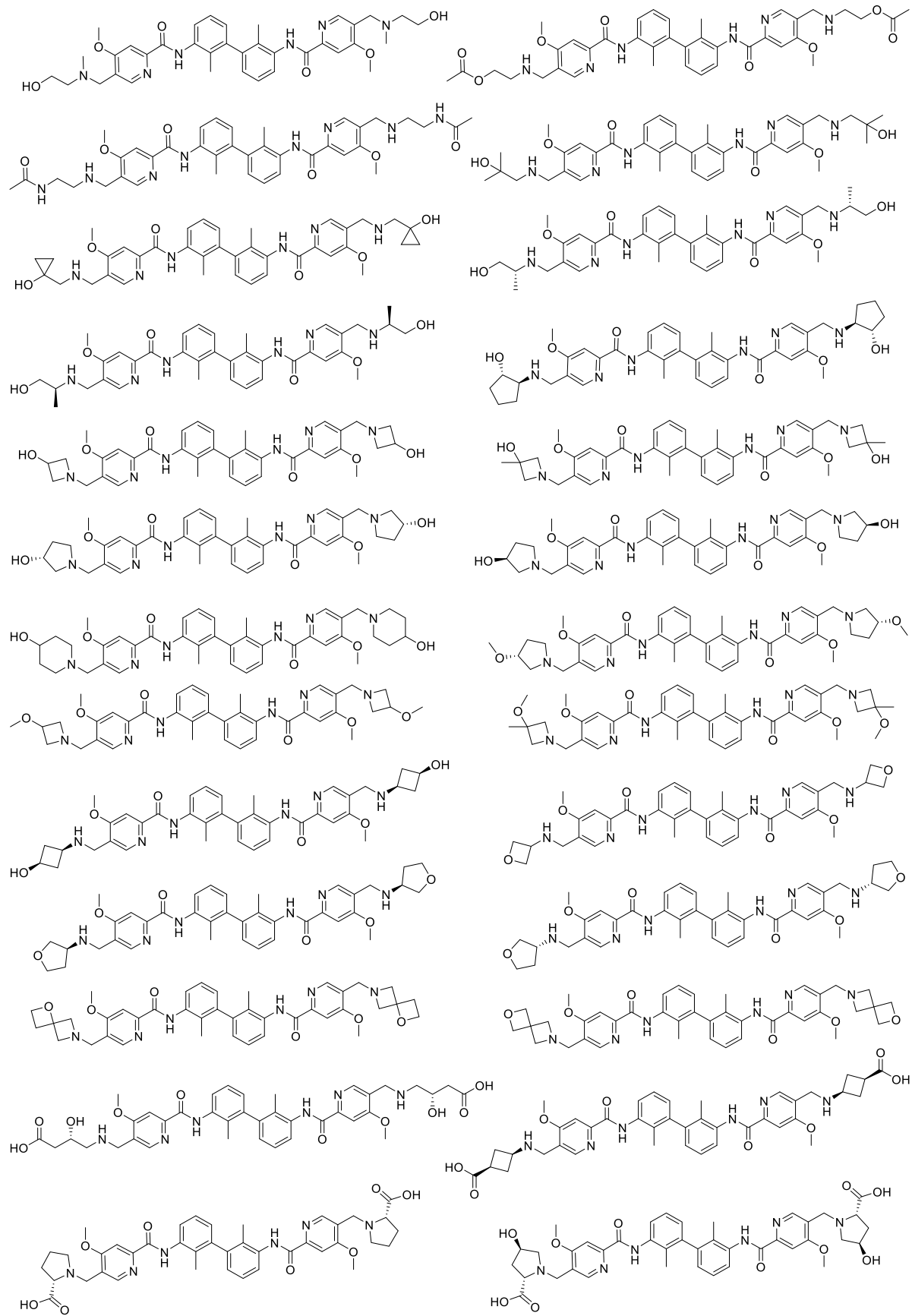
cycloalkyloxy, 3-6 membered heterocyclyl, 3-6 membered heterocyclyloxy, phenyl, phenoxy, 5-8 membered heteroaryl, 5-8 membered heteroaryloxy, amino, monoalkylamino, dialkylamino and C₁₋₄ alkanoyl; and

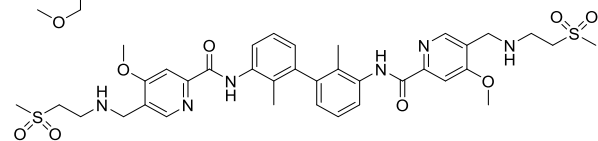
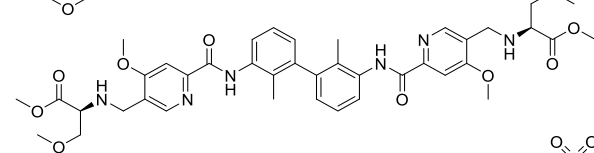
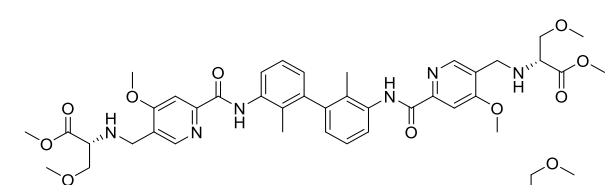
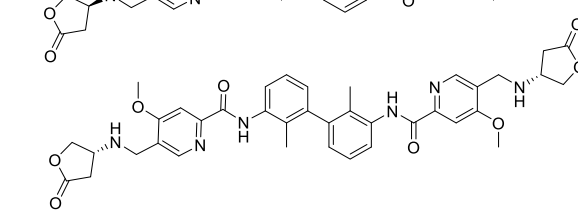
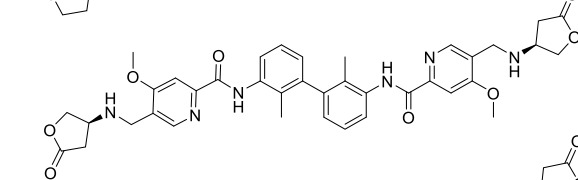
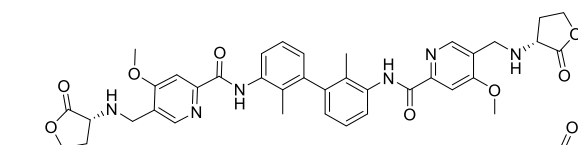
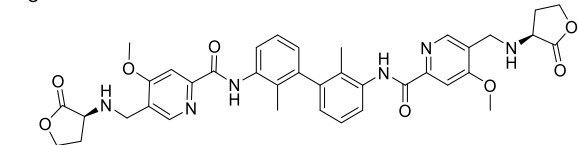
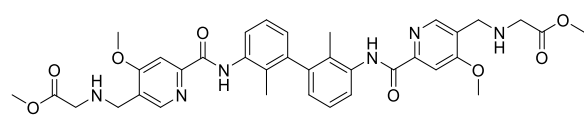
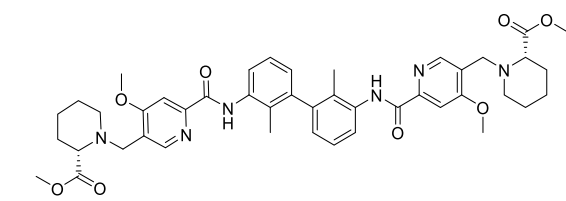
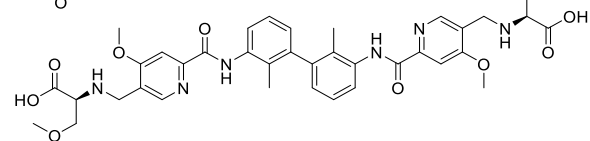
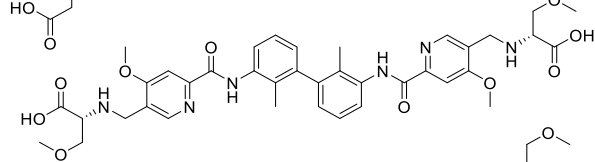
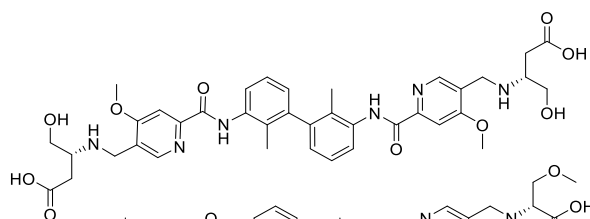
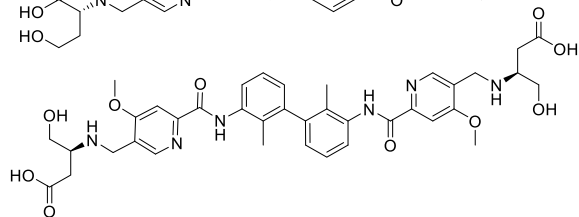
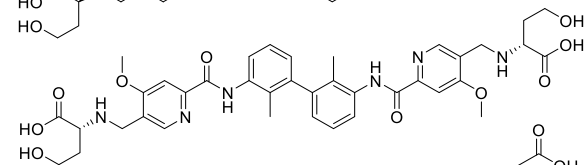
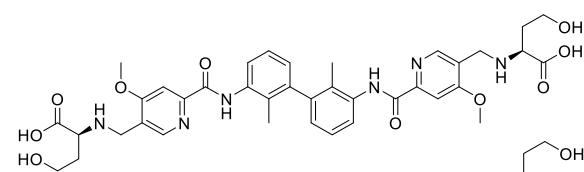
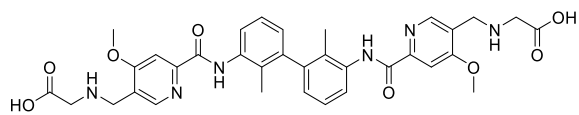
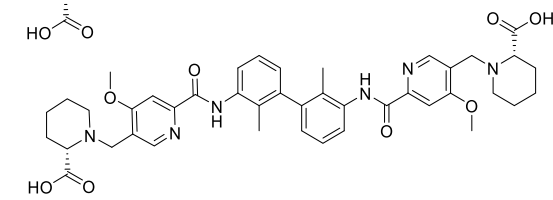
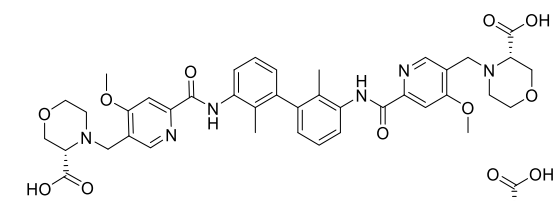
r is independently 0, 1 or 2.

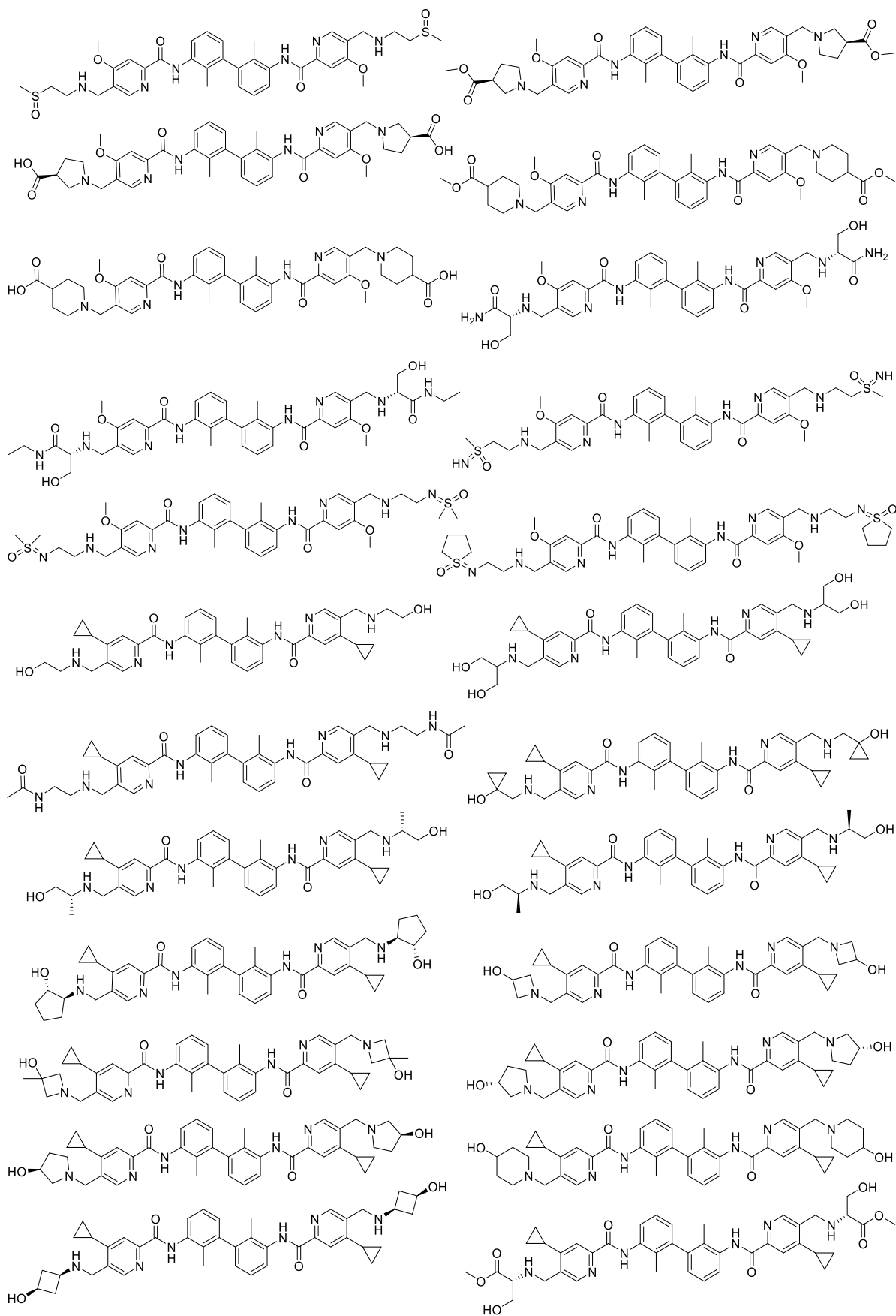
5. The compound of formula (III), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein the compound is selected from the following compounds:

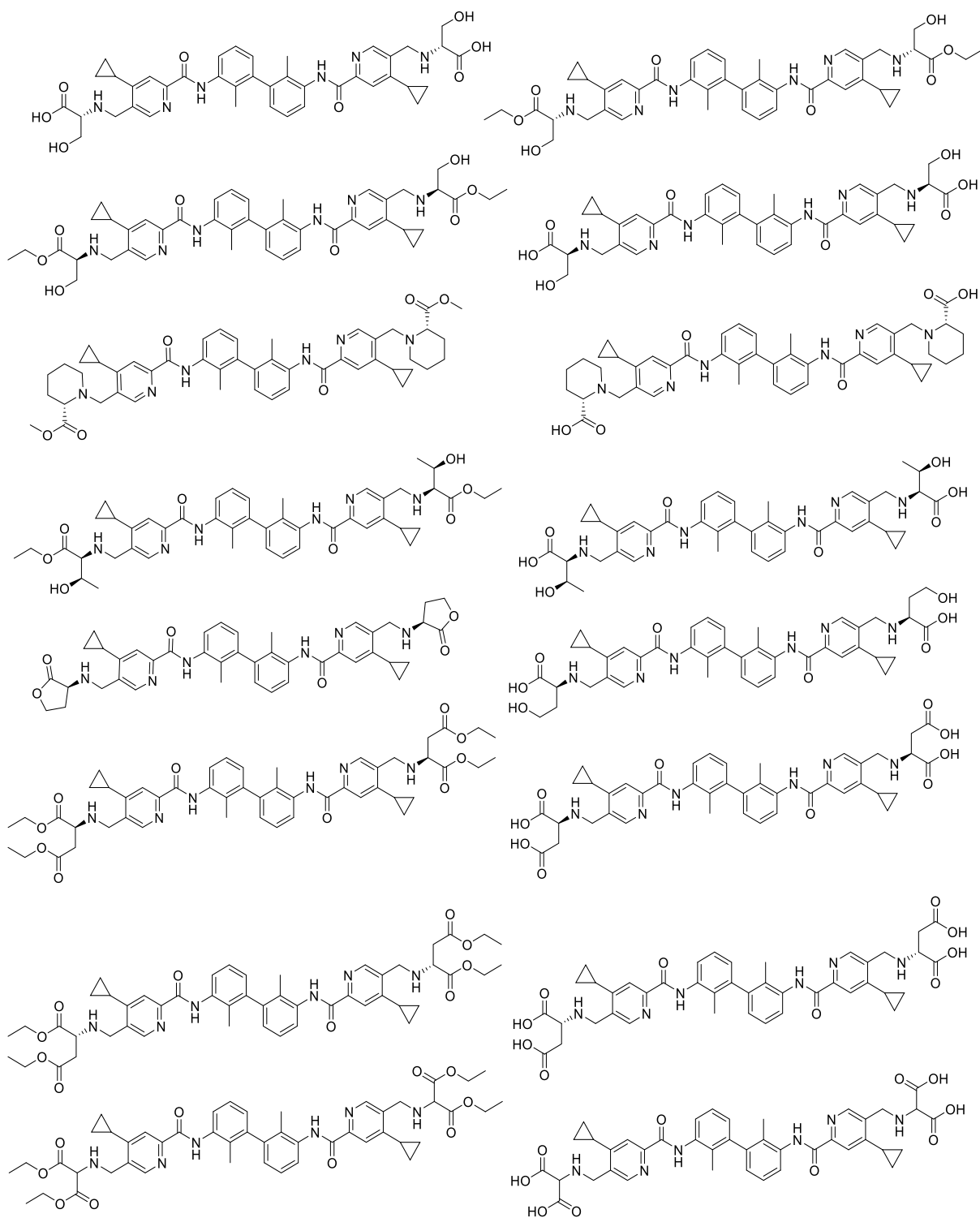


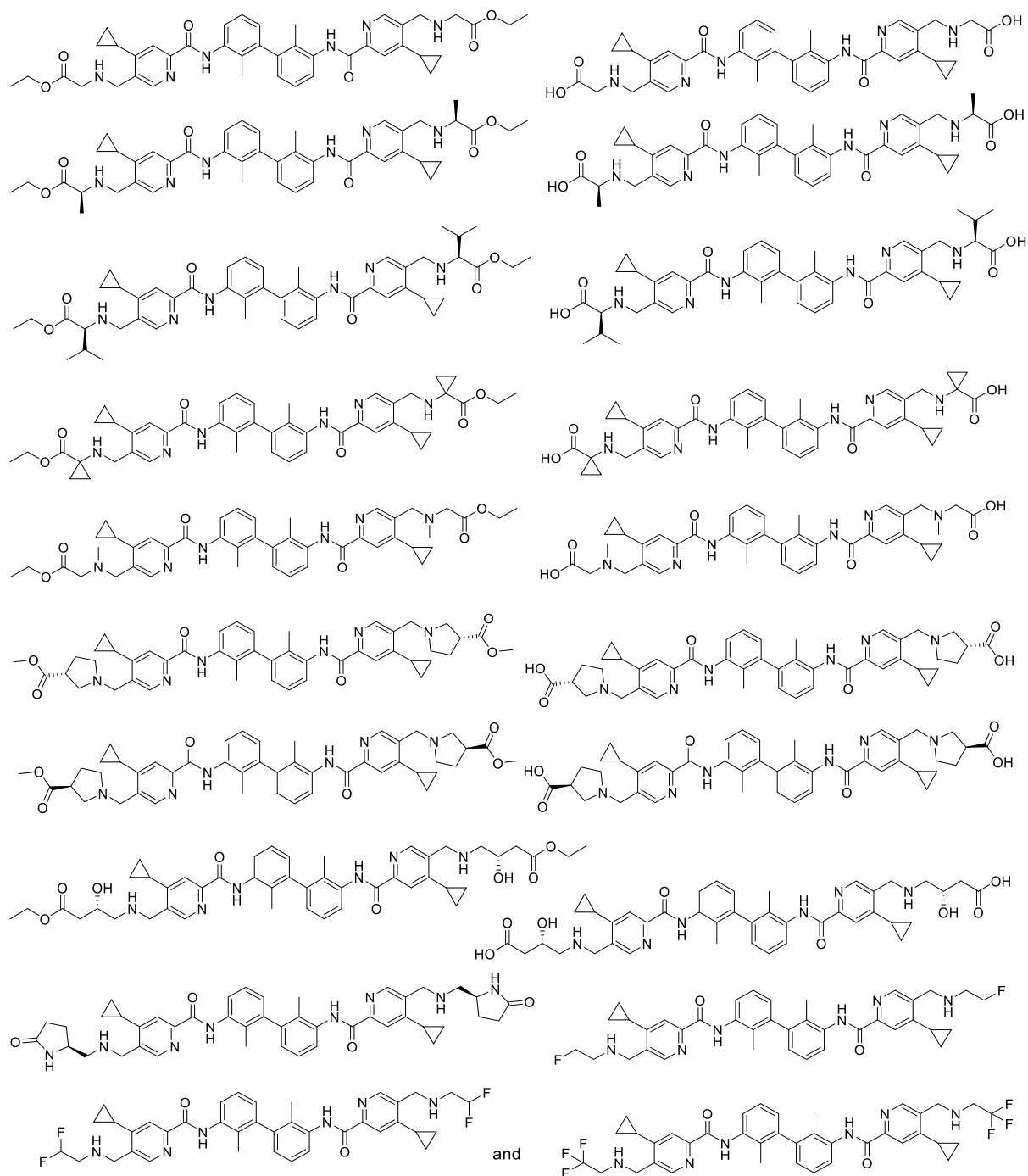




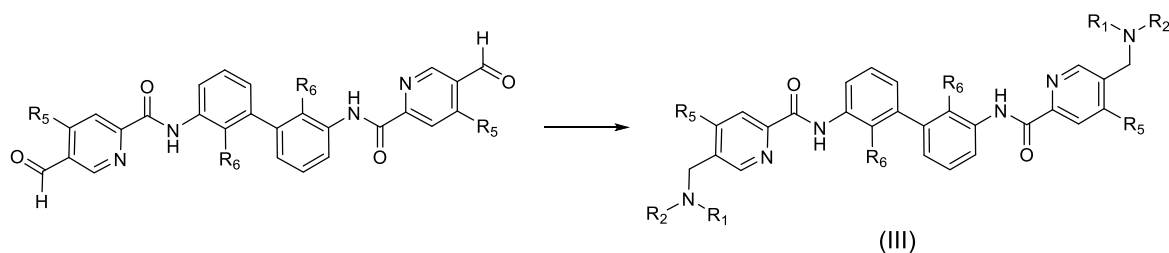








6. A process for preparing the compound of formula (III), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 5, comprising the following steps:



wherein R₁, R₂, R₅ and R₆ are defined as in claim 1.

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

8. Use of the compound of formula (III), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 5 or the pharmaceutical composition of claim 7 in the preparation of a medicament for preventing and/or treating PD-1/PD-L1 protein-protein interaction related disease,

wherein the PD-1/PD-L1 protein-protein interaction related disease is cancer or tumor, immune-related disease and disorder, communicable disease, infectious disease or metabolic disease.

9. The use of claim 8, wherein the infectious disease is bacterial infectious disease, viral infectious disease or fungal infectious disease.

10. The use of claim 8, wherein, the cancer or tumor is selected from lymphoma, sarcoma, melanoma, glioblastoma, synovioma, meningioma, biliary tract tumor, thymic tumor, neuroma, seminoma, nephroblastoma, pleomorphic adenoma, hepatocellular papilloma, renal tubule adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma, fibroma, central nervous system tumor, rhachiophyma, brain stem glioma, pituitary adenoma, multiple myeloma, ovarian tumor, myelodysplastic syndrome or mesothelioma, prostate cancer, recurrent prostate cancer or prostate cancer having developed resistance to existing medicaments, thyroid cancer, parathyroid cancer, anal cancer, testicular cancer, urethral carcinoma, penile cancer, bladder cancer, ureteral cancer, uterine cancer, ovarian cancer, fallopian tube cancer, endometrial cancer, cervical cancer, vaginal cancer, vulvar cancer, adrenal cancer, Merkel cell carcinoma, embryonal carcinoma, chronic or acute leukemia, bronchial carcinoma, esophageal cancer, nasopharyngeal carcinoma, hepatocellular carcinoma, renal cell carcinoma, small cell lung cancer, basal cell carcinoma, lung cancer, breast cancer, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, squamous non-small cell lung cancer, non-squamous non-small cell

lung cancer, rectal cancer, colon cancer, colorectal cancer, gastric cancer, pancreatic cancer, head and neck squamous cell carcinoma, head and neck cancer, gastrointestinal cancer, bone cancer, skin cancer, small intestine cancer, endocrine cancer, renal pelvic carcinoma, epidermoid carcinoma, abdominal wall carcinoma, renal cell carcinoma, transitional cell carcinoma, choriocarcinoma, or metastatic tumor;

the immune-related disease and disorder is selected from rheumatic arthritis, renal failure, lupus erythematosus, asthma, psoriasis, ulcerative colitis, pancreatitis, allergy, fibrosis, anemia, fibromyalgia, Alzheimer's disease, congestive heart failure, stroke, aortic valve stenosis, arteriosclerosis, osteoporosis, Parkinson's disease, infection, Crohn's disease, ulcerative colitis, allergic contact dermatitis and eczema, systemic sclerosis or multiple sclerosis;

the communicable disease or infectious disease is selected from sepsis, liver infection, HIV, hepatitis A, hepatitis B, hepatitis C, hepatitis D, herpes virus, papillomavirus or influenza;

the metabolic disease is selected from diabetes, diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, hypoglycemia, gout, malnutrition, vitamin A deficiency, scurvy, vitamin D deficiency or osteoporosis.

11. The use of claim 10, wherein said lymphoma is selected from the group consisting of lymphocytic lymphoma, primary central nervous system lymphoma, T cell lymphoma, diffuse large B cell lymphoma, follicle center lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma and primary mediastinal large B cell lymphoma;

said sarcoma is selected from the group consisting of Kaposi's sarcoma, fibrosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, leiomyosarcoma, rhabdomyosarcoma, soft tissue sarcoma, angiosarcoma or lymphangiosarcoma;

said chronic or acute leukemia is selected from the group consisting of acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic granulocytic leukemia and chronic lymphoblastic leukemia.

12. The compound of formula (III), the stereoisomer or pharmaceutically acceptable salt thereof of any one of claims 1 to 5 or the pharmaceutical composition of claim 7 for use as a medicament for preventing and/or treating PD-1/PD-L1 protein-protein interaction related cancer or tumor, immune-related disease and disorder, communicable disease, infectious disease or metabolic disease.