

**USE OF PHARMACEUTICAL COMPOSITION COMPRISING COMPOUND HAVING
BIS(AZANYLYLIDENE)
SULFONYL STRUCTURE FOR TREATING ANEMIA-RELATED DISEASES**

5 TECHNICAL FIELD

The present disclosure belongs to the field of pharmaceutical technology, and specifically relates to use of a pharmaceutical composition containing a diazanylidenesulfonyl structure compound in treating anemia-related diseases.

BACKGROUND

10 Under normal physiological conditions, the human body carries and delivers oxygen to tissues and organs through the hemoglobin in mature red blood cells. Glycolysis plays an important role in maintaining the lifespan, morphology, and function of red blood cells (RBCs).

The β -thalassemia is an autosomal-recessive genetic disease. Due to point mutations or deletions of the β -chain gene, the synthesis of the β -chain is partially or completely inhibited, resulting in an imbalance in the ratio of the α -chain to the β -chain. The α -chains accumulate near the cell membrane to form insoluble haemichromes and result in a reduction in the total oxygen-carrying capacity of the RBC and meanwhile an increase in free heme and iron, which increase the level of reactive oxygen species (ROSs) and oxidize cell membrane proteins and lipids, leading to cytolysis and premature apoptosis and inhibiting RBC differentiation and maturation stages. Therefore, RBCs in patients with β -thalassemia consume more ATP, which is a key factor in the shortened lifespan and increased hemolysis of RBCs (*Int J Mol Sci* 22, 7229 (2021)). The patients with β -thalassemia have different clinical manifestations, ranging from asymptomatic, non-transfusion-dependent β -thalassemia (NTDT) to transfusion-dependent β -thalassemia (TDT), which are mainly related to the degree of β -chain deletion. Patients with TDT produce little HbA and usually develop anemia after HbF is converted to HbA. It is estimated that about 5% of the world's population has at least one β -thalassemia gene variation, and there are approximately 300,000 patients with β -thalassemia worldwide, who are distributed along the Mediterranean coast and throughout Southeast Asia (*N Engl J Med* 371, 1908-1916 (2014)), and mainly distributed in the south of the Yangtze River in China. In 2017, a Meta-analysis result showed that the incidence rate of β -thalassemia in Chinese mainland was 2.21% (*Sci Rep* 7, 920 (2017)).

Sickle cell anemia (SCD) is an autosomal inherited hemoglobinopathy. Since glutamic acid at position 6 of the β -peptide chain is replaced by valine, hemoglobin S (HbS) is prone to polymerization to form a sickle-shaped red blood cell when it is deoxygenated. Clinical manifestations include chronic hemolytic anemia, organ and tissue damage caused by chronic ischemia, splenic infarction, susceptibility to infection, and vaso-occlusive crises (VOCs) (*Lancet* 376, 2018-2031 (2010)). SCD mutated genes are distributed around the world, including African Americans (about 7%-10%), sub-Saharan Africa (30%), Mediterranean countries (especially Greece), Middle East (0.2%-27%) and India (13%), and the like districts (*J Neonatal Screen* 4, 31 (2018)). To sum up, the global prevalence of SCD is estimated to be approximately 300 million people (*Engl J Med* 375, 435-442 (2016)). In patients with β -thalassemia and SCD, the imbalance of an α -non- α -chain ratio leads to ineffective erythropoiesis (IE), triggers the

apoptosis of erythroid precursors, leading to anemia, splenomegaly and decreased production of hepcidin, and leading to systemic iron overload. IE is the main pathogenesis and pathological feature of β -thalassemia. In the bone marrow of a patient with β -thalassemia, the content of the erythroid precursors is about 6 times higher than that of normal people, and the apoptosis rate is about 4 times higher than that of normal people (*Int J Mol Sci* 22, 7229 (2021)). Moreover, the life span of circulating red blood cells in the patients with SCD is shortened, and late erythroblast death also occurs in the body.

Pyruvate kinase deficiency (PKD) is a hereditary functional deficiency of an enzyme in the red blood cell glycolysis pathway, resulting in non-spherocytic hemolytic anemia. All of the above are autosomal recessive genetic disorders, causing decreased hemoglobin (Hb), altered oxygen-carrying function, shortened red blood cell lifespan, and congenital anemia.

Myelodysplastic syndrome (MDS) is a group of heterogeneous myeloid clonal diseases originating from hematopoietic stem cells, characterized by abnormal differentiation and development of myeloid cells, manifested as ineffective hematopoiesis, progressive cytopenia, and hematopoietic failure. Among them, the main symptom of patients with lower-risk myelodysplastic syndrome (LR-MDS) is anemia, characterized by abnormal hematopoietic function and transformation to high-risk acute myeloid leukemia (AML).

For anemia-related diseases such as β -thalassemia, sickle cell anemia (SCD), pyruvate kinase deficiency (PKD), and lower-risk myelodysplastic syndrome (LR-MDS), hematopoietic stem cell (HSC) transplantation is currently the only curative measure. However, it is limited by the availability of donors, post-transplantation immunosuppression, and the relatively higher cost of treatment. The proportion of patients suitable for this therapy is very small. Supportive treatments include blood transfusion, folic acid supplementation, splenectomy, and the administration of iron chelators to reduce iron overload, etc. To improve IE caused by α -non- α -chain ratio imbalance, treatment means currently being studied include three aspects of the gene, protein, and small molecule compound treatments.

In terms of gene treatment, it was reported in 2018 that 22 cases of TDT patients used autologous HSCs with LentiGlobin BB305 vectors encoding T87Q variant, with significant clinical benefits, but the patients were not completely cured (*N Engl J Med* 378, 1479-1493 (2018)). Moreover, based on CRISPR-Cas9 technology, CTX001 is used for inhibiting BCL11A to induce HbF, which can reduce the number of blood transfusion in patients with severe SCD (*N Engl J Med* 384, 252-260 (2021)).

The recombinant fusion protein Luspatercept (ACE-536) was approved for the treatment of adult patients with TDT in 2019. Luspatercept can bind to transforming growth factor TGF β superfamily ligands, inhibit a SMAD2/3 pathway, promote RBC maturation, and reduce the number of blood transfusions for the patients (*J Cell Mol Med* 24, 6162-6177 (2020)). Crizanlizumab, a monoclonal antibody against P-selectin that has been approved by FDA, is used for reducing the frequency of occurrence of VOCs by reducing the interaction between endothelial cells and circulating blood cells, but it cannot alter HbS aggregation (*J Pain Res* 14, 849-856 (2021)).

Although there are currently many treatment options mentioned above, these treatment manners, including hematopoietic stem cell transplantation, gene treatment, recombinant fusion protein treatment, and treatment with blood transfusion combined with iron chelators, generally have shortcomings such as the risk of surgical complications, high economic burden, and impact on the patient's quality of life.

There is still a huge number of unmet needs. In contrast, the chemical small molecule drug therapy has unique clinical advantages.

Among small molecule compounds, the Janus kinase 2 inhibitor Ruxolitinib can improve IE and reduce splenomegaly in a β -thalassemia mouse model (*Blood* 131, 263-265 (2018)). Bitopertin (RO-4917838), an orally available potent and highly selective glycine transporter 1 inhibitor, can improve anemia and hemolysis in patients with β -thalassemia and improve RBC survival rate *in vivo* (*Br J Haematol* 194, 474-477 (2021)). VIT-2763, an orally active small-molecule ferroportin inhibitor, blocks iron efflux by inhibiting the binding of hepcidin to ferroportin (*J Clin Invest* 130, 491-506 (2020)). Inducing continuous production of HbF can alleviate the clinical symptoms of patients with β -chain abnormalities, such as hydroxyurea (HU), which is clinically used in the treatment of SCD and can stimulate HbF production and reduce HbS aggregation. However, HU will inhibit a bone marrow function. IMR-687, a phosphodiesterase (PDE9) inhibitor, has an obvious therapeutic effect in a SCD preclinical model by inhibiting PDE9, increasing intracellular cGMP levels and stimulating HbF production (*Haematologica* 105, 623-631 (2020)).

A pyruvate kinase (PK) is a key enzyme in glycolysis, which catalyzes the conversion of phosphoenolpyruvate into enolpyruvate and produces adenosine triphosphate (ATP). The effective generation of ATP can maintain red blood cell function and membrane integrity and meet the energy needs of clearing excess globin chains. When the ATP supply cannot meet the metabolic needs of thalassemia red blood cells, it will cause premature cell death, ultimately leading to ineffective erythropoiesis and hemolysis. Therefore, by stimulating PKR to increase ATP in red blood cells, it is expected to play a positive role in the treatment of patients with hemoglobinopathies such as PKR-deficient β -thalassemia, sickle cell anemia (SCD), pyruvate kinase deficiency (PKD) and lower-risk myelodysplastic syndrome (LR-MDS).

Currently, research literatures on small molecule drugs targeting PKR have been disclosed one after another. However, compared with other popular targets, there are still relatively few studies on the small molecule drugs, which are mainly as follows:

Mitapivat (AG-348), which is an oral small-molecule allosteric agonist, has shown efficacy and safety in clinical trials in patients with PKR deficiency (*N Engl J Med* 381, 933-944 (2019)). Mitapivat was approved for marketing by the US FDA in February 2022 for the treatment of anemia in adults with PK deficiency. Phase III clinical studies are currently underway for thalassemia and sickle cell anemia. Completed Phase II clinical studies have shown good efficacy. At week 12, 92.3% of patients achieved an increase in HGB of 1.0 g/dL, with an average increase of 1.34 g/dL, and improved hemolytic and erythropoietic markers. Studies have shown that LR-MDS patients have glycolytic dysfunction and acquired PK deficiency. PK activation can increase red blood cell energy and solve the problem of ineffective erythropoiesis. Phase II clinical studies of the second-generation compound AG-946 for the anemia symptoms of LR-MDS patients are underway.

FORMA Therapeutics Inc discloses a pyrrolopyrrole compound as a PKR agonist in WO2018175474 and WO2020061255.

Global Blood Therapeutics Inc discloses a pyrrolidinopyrazole compound as a pyruvate kinase activator in WO2021202796.

Agios Pharmaceuticals Inc discloses an azetidine arylsulfonamide derivative compound as a pyruvate

kinase modulator in WO2012083246, WO2011002817, WO2012092442, WO2014139325, etc.

SUMMARY OF THE INVENTION

The applicant of the present disclosure previously provided a novel compound containing a diazanylidenesulfonyl structure in international application PCT/CN2022/140731 (international filing
5 date December 21, 2022). The entire contents of the prior international application PCT/CN2022/140731 are hereby incorporated into the present disclosure as a part thereof.

Based on the novel compound disclosed in PCT/CN2022/140731, the inventors have conducted further research and provided novel use of pharmaceutical composition containing the novel compound in the treatment and prevention of anemia-related diseases.

10 Although the entire contents of the prior international application PCT/CN2022/140731 are incorporated herein by reference, for the sake of clarity and completeness, the present disclosure further describes the novel compound in detail through the structural descriptions below and the preparation and characterization of the specific examples that follow. The compound of the general formula and the compounds of the specific examples described in international application PCT/CN2022/140731 are
15 referred to herein as "compound(s) of the present disclosure".

As confirmed by the biological activity test of the present application, the compound of the present disclosure has good agonist activity on PKR in in vitro enzymatic test, and can also significantly activate PKR activity in red blood cells of healthy people and patients with β -thalassemia in ex vivo test, and significantly increase the concentration of biomarker ATP and reduce the concentration of
20 2,3-DPG. The same pharmacodynamic effect was also observed in further in vivo test in wild-type mice. In addition, in anemic mouse models, hemoglobin content can also be increased, ATP concentration can be increased, 2,3-DPG concentration can be reduced, and oral absorption is good in rats, mice, and dogs. Therefore, it is expected that the compound of the present disclosure has important development value and application potential in the treatment or prevention of anemia-related diseases
25 such as β -thalassemia, sickle cell anemia (SCD), pyruvate kinase deficiency (PKD), and myelodysplastic syndrome (MDS).

Thus, in a first aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient for use as a PKR agonist.

30 In a second aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient for use in preventing or treating anemia-related disease.

In a third aspect, the present disclosure provides use of a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient in the preparation of a
35 medicament for preventing or treating anemia-related disease.

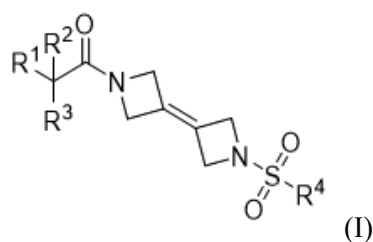
In a fourth aspect, the present disclosure provides a method for preventing or treating anemia-related disease, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient.

40 In particular, the anemia-related disease mentioned above include pyruvate kinase deficiency (PKD),

myelodysplastic syndrome (MDS), hemoglobinopathy, sickle cell anemia (SCD), β -thalassemia, hereditary non-spherocytic hemolytic anemia, hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, paroxysmal nocturnal hemoglobinuria, acquired hemolytic anemia, congenital anemia or anemia of chronic disease; preferably, the anemia-related disease is pyruvate kinase deficiency (PKD), myelodysplastic syndrome (MDS), sickle cell anemia (SCD) or β -thalassemia, and the myelodysplastic syndrome (MDS) may further be lower-risk myelodysplastic syndrome (LR-MDS).

Detailed description of the present disclosure:

In one embodiment, the compound of the present disclosure according to the first, second, third and fourth aspects of the present disclosure is selected from a compound of formula I, or an isomer, pharmaceutically acceptable salt or solvate thereof:



wherein:

R^1 , R^2 and R^3 are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b, -SR^b, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f or -C(O)OR^g, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -SR^b, -NO₂, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f and -C(O)OR^g;

or, R^1 and R^2 , R^1 and R^3 , or R^2 and R^3 together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, -(C₅-C₈)spirocyclyl, 5-8 membered spiroheterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, or 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S;

R^4 is -NH₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b, -SR^b, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f, -C(O)OR^g or -NR^c(CR^hRⁱ)_n-R^a, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or fused ring group is optionally substituted by one or more

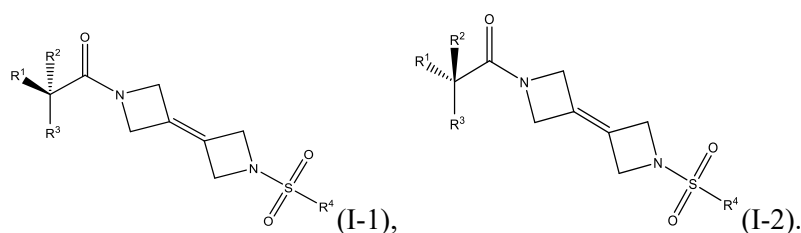
substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -SR^b, -NO₂, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f and -C(O)OR^g;

t is 0, 1, 2 or 3;

R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and Rⁱ at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H or -C(O)OH, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H, -C(O)OH, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl and 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, or wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or fused ring group is optionally substituted by one or more substituents selected from: -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH; or R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and Rⁱ at each occurrence are independently -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH;

or, any two groups on adjacent atoms selected from R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and Rⁱ together with atoms to which they are attached optionally bind to form C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, (C₃-C₈)cycloalkyl, or 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, which is optionally substituted by one or more R^a.

In some embodiments, the compound of the present disclosure according to the first, second, third and fourth aspects of the present disclosure are selected from specific isomeric compounds of the aforementioned formula I, having formula I-1 or I-2,



In some embodiments, in the aforementioned compounds of formula I, I-1 or I-2 of the present disclosure, R¹ and R² can be further independently selected from the following:

In one embodiment,

R¹ and R² are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group

containing 0-4 heteroatoms independently selected from O, N and S, -OR^b or -NR^cR^d, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

- 5 or, R¹ and R² together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, and 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S.

In another embodiment,

R¹ and R² are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b or -NR^cR^d, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

- 25 or, R¹ and R² together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, and 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S.

In another embodiment,

- 35 R¹ and R² are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆) linear alkyl, -(C₁-C₆) branched alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 7-14 membered bicyclic or tricyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b or -NR^cR^d, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a, -OR^b, and -NR^cR^d;

or, R¹ and R² together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, or 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, and -(C₁-C₆)alkyl.

In another embodiment,

10 R¹ and R² are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆) linear alkyl, -(C₁-C₆) branched alkyl, -(C₃-C₆)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a, -OR^b, and -NR^cR^d;

15 or, R¹ and R² together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, and -(C₁-C₆)alkyl.

In another embodiment,

R² is -H, -F, -Cl or -Br;

R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, -(CH₂)_qCH₃, -(CH₂)_qOH, -CH(OH)(CH₂)_qCH₃, -C(OH)((CH₂)_qCH₃)₂,
 25 , -(CH₂)_qNH₂, -(CH₂)_qNH(CH₂)_qCH₃, -(CH₂)_qN((CH₂)_qCH₃)₂, 3-6 membered heterocycloalkyl containing 1 N atom, or -(C₁-C₆)alkyl substituted by 3-6 membered heterocycloalkyl containing 1 N atom;

q at each occurrence is independently 0, 1, 2, 3 or 4;

or, R¹ and R² together with atoms to which they are attached may optionally bind to form a
 30 cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, tetrahydrofuran, tetrahydropyran, morpholine, dioxane or 2,3-dihydrobenzofuran ring; or, R¹ and R² together with the atoms to which they are attached may optionally bind to form a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, tetrahydrofuran, tetrahydropyran, morpholine, dioxane, a 2,3-dihydrobenzofuran ring, or tetrahydro-2H-pyran.

35 In another embodiment,

R² is -H, -F, -Cl or -Br;

R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, , , , , , ,  or ;

or, R¹ and R² together with the atoms to which they are attached may optionally bind to form ; or,

R¹ and R² together with the atoms to which they are attached may optionally bind to form .

In another embodiment,

R² is -H, -F, -Cl or -Br;

- 5 R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, -CH₃, -CH(OH)CH₃, -(CH₂)_qCH₃, -(CH₂)_qOH, -CH(OH)(CH₂)_qCH₃, -C(OH)((CH₂)_qCH₃)₂, -C(OH)((CH₂)_qCH₃)(CH₃), -C(OH)(CH₃)₂, HO-, HO-, -CH₂F, -CHF₂, -(CH₂)_qCH₂F, -(CH₂)_qCHF₂, -CH₂Cl, -CHCl₂, -(CH₂)_qCH₂Cl, -(CH₂)_qCHCl₂, -(CH₂)_qNH₂, -NHCH₃, -NH(CH₂)_qCH₃, -(CH₂)_qNHCH₃, -(CH₂)_qNH(CH₂)_qCH₃, -N(CH₃)₂, -N((CH₂)_qCH₃)₂, -(CH₂)_qN(CH₃)((CH₂)_qCH₃), -(CH₂)_qN(CH₃)₂, -(CH₂)_qN((CH₂)_qCH₃)₂, 3-6 membered heterocycloalkyl containing 1 N atom, or -(C₁-C₆)alkyl substituted by 3-6 membered heterocycloalkyl containing 1 N atom;

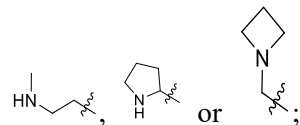
q at each occurrence is independently 1, 2, 3 or 4;

- or, R¹ and R² together with atoms to which they are attached optionally bind to form a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, oxetane, tetrahydrofuran, tetrahydropyran, morpholine, dioxane, a 2,3-dihydrobenzofuran ring, or tetrahydro-2H-pyran.

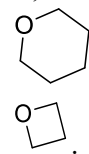
In another embodiment,

R² is -H, -F, -Cl or -Br;

R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, HO-, HO-, HO-, HO-, HO-, F-, H-, N-,



- 20 or, R¹ and R² together with the atoms to which they are attached may optionally bind to form  or



- In some embodiments, in the compounds of formula I, I-1 or I-2 of the present disclosure, on the basis that R¹ and R² are independently made any of the selections and combinations as described above, R³ can be further independently selected from the follows.

In one embodiment,

- R³ is -H, halogen, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more

substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, and 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S.

In another embodiment,

R³ is -H, halogen, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered bicyclic or tricyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, and 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S.

In another embodiment,

R³ is -H, -F, -Cl, -Br, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered bicyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a and -OR^b;

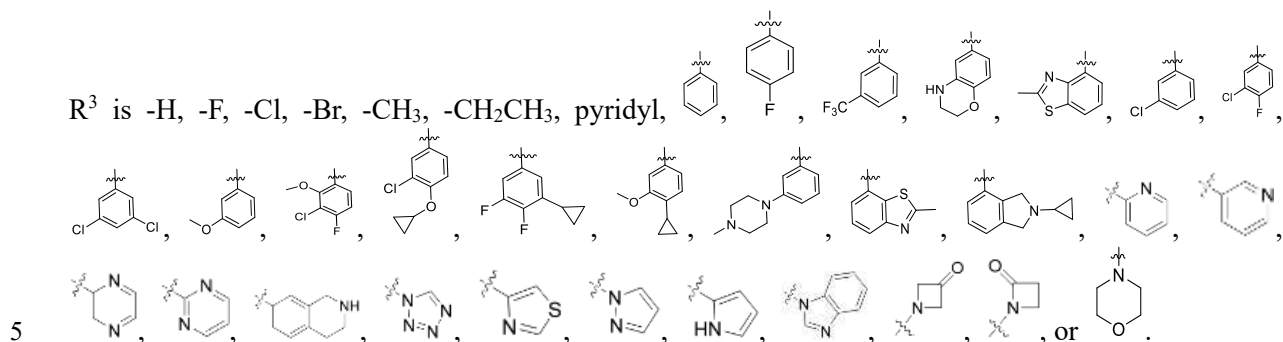
R^a and R^b at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, and -(C₁-C₆)alkyl.

In another embodiment,

R³ is -H, -F, -Cl, -Br, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, pyridyl, phenyl, benzothiazolyl, benzomorpholinyl, or benzopyrrolidinyl, wherein the pyridyl, phenyl, benzothiazolyl, benzomorpholinyl, or benzopyrrolidinyl is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, -O-(C₁-C₆)alkyl, -O-(C₃-C₆)cycloalkyl,

piperazinyl, and piperazinyl substituted by any number of halogen or $-(C_1-C_6)$ alkyl.

In another embodiment,



In another embodiment,

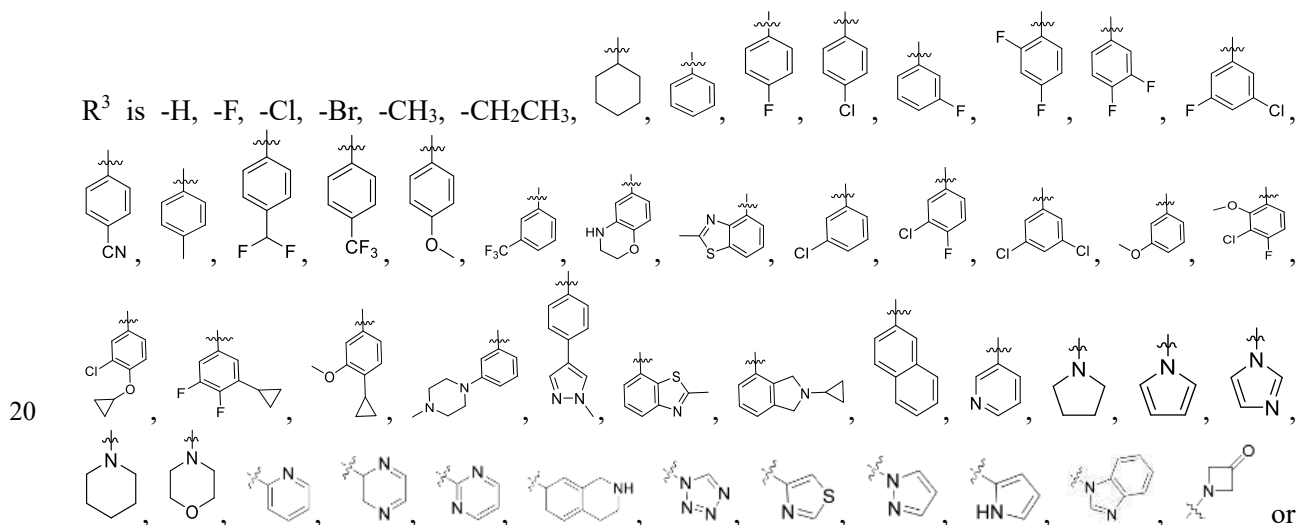
R^3 is -H, -F, -Cl, -Br, $-(C_1-C_6)$ alkyl, $-(C_3-C_6)$ cycloalkyl, pyridyl, phenyl, naphthyl, benzothiazolyl,

benzomorpholinyl, benzopyrrolidinyl or , wherein the pyridyl, phenyl, benzothiazolyl,

10 benzomorpholinyl, benzopyrrolidinyl, or  is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, $-(C_1-C_6)$ alkyl, $-(C_3-C_6)$ cycloalkyl, $-O-(C_1-C_6)$ alkyl, $-O-(C_3-C_6)$ cycloalkyl, $-(C_1-C_6)$ haloalkyl, $-(C_3-C_6)$ halocycloalkyl, $-O-(C_1-C_6)$ haloalkyl, $-O-(C_3-C_6)$ halocycloalkyl, pyrazolyl, pyrazolyl substituted by any number of halogen or $-(C_1-C_6)$ alkyl, piperazinyl, piperazinyl substituted by any number of halogen or $-(C_1-C_6)$ alkyl; and

15 the ring  is 3-6 membered saturated or unsaturated heterocyclyl connected through an N atom, and in addition to the N atom, the heterocyclyl optionally contains 1-2 heteroatoms independently selected from O, N and S.

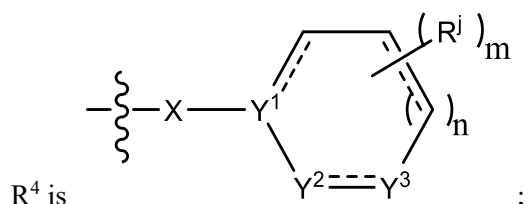
In another embodiment,





In some embodiments, in the compounds of formula I, I-1 or I-2 of the present disclosure, on the basis that R^1 , R^2 and R^3 are independently made any of the selections and combinations as described above, R^4 can be further selected from the following:

5 In a first kind of embodiments:



X is a chemical bond, $-(CR^hR^i)_t-$, $-NR^c(CR^hR^i)_t-$ or $-O-$; wherein R^c , R^h , R^i and t are optionally as defined anywhere they are occurred in the present disclosure;

===== represents a single bond or double bond;

10 Y^1 is N, C or CH;

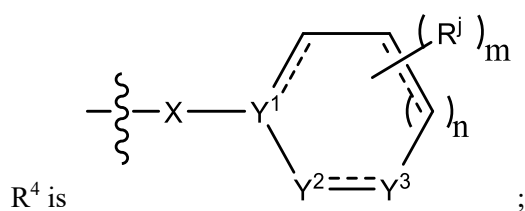
Y^2 and Y^3 are each independently N, CH_2 or CH, and Y^2 and Y^3 are not both N at the same time;

each R^j is independently -H, halogen, -OH, -NH₂, -CN, -NO₂, $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkoxy$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_3-C_8)cycloalkyl$, $-(C_4-C_8)cycloalkenyl$, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C_6-C_{14} aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H or -C(O)OH, wherein each of the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -H, =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H, -C(O)OH, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C_6-C_{14} aryl or 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or wherein each of the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH; or, each R^j is independently and optionally -O- $(C_3-C_6)cycloalkyl$, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH;

m is selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2.

In some of the first kind of embodiments,



X is a chemical bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{NHCH}_2-$, $-\text{NHCH}_2\text{CH}_2-$ or $-\text{O}-$;

----- represents a single bond or double bond;

Y^1 is N, C or CH;

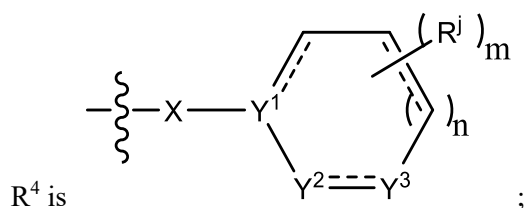
- 5 Y^2 and Y^3 are each independently N, CH_2 or CH, and Y^2 and Y^3 are not both N at the same time;

each R^j is independently -H, halogen, -OH, $-\text{NH}_2$, -CN, $-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-(\text{C}_1-\text{C}_6)\text{alkoxy}$, $-(\text{C}_1-\text{C}_6)\text{alkyl}$ or $-(\text{C}_1-\text{C}_6)\text{alkoxy}$ substituted by any number of halogen, oxazolyl, thiazolyl and triazolyl;

m is selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2.

- 10 In some of the first kind of embodiments,



X is a chemical bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{NHCH}_2-$, $-\text{NHCH}_2\text{CH}_2-$ or $-\text{O}-$;

----- represents a single bond or double bond;

Y^1 is N, C or CH;

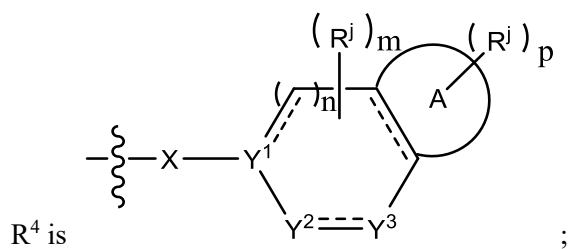
- 15 Y^2 and Y^3 are each independently N, CH_2 or CH, and Y^2 and Y^3 are not both N at the same time;

each R^j is independently -H, halogen, -OH, $-\text{NH}_2$, -CN, $-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$, $-(\text{C}_1-\text{C}_6)\text{alkoxy}$, $-\text{O}-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$, $-(\text{C}_1-\text{C}_6)\text{alkyl}$ substituted by any number of halogen, $-(\text{C}_1-\text{C}_6)\text{alkoxy}$ substituted by any number of halogen, $-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$ substituted by any number of halogen, $-\text{O}-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$ substituted by any number of halogen, oxazolyl, thiazolyl and triazolyl;

- 20 m is selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2.

In a second kind of embodiments:



X is a chemical bond, $-(CR^hR^i)_t-$, $-NR^c(CR^hR^i)_t-$ or $-O-$; wherein R^c , R^h , R^i and t are optionally as defined anywhere they are occurred in the present disclosure;

===== represents a single bond or double bond;

5 Y^1 is N, C or CH;

Y^2 and Y^3 are each independently N, CH_2 or CH, and Y^2 and Y^3 are not both N at the same time;

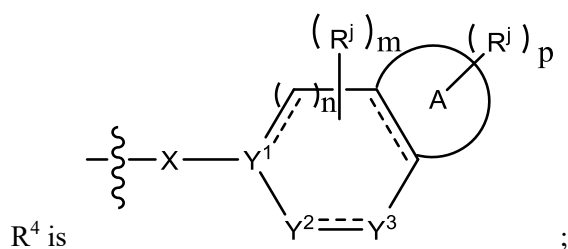
each R^j is independently -H, halogen, -OH, -NH₂, -CN, -NO₂, $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkoxy$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_3-C_8)cycloalkyl$, $-(C_4-C_8)cycloalkenyl$, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H or -C(O)OH, wherein each of the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H, -C(O)OH, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl or 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or wherein each of the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH; or, each R^j is independently and optionally =O, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH;

m and p are independently selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

ring A is $(C_3-C_8)cycloalkyl$, $(C_4-C_8)cycloalkenyl$, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S.

In some of the second kind of embodiments,



X is a chemical bond, -CH₂-, -CH₂CH₂-, -NHCH₂-, -NHCH₂CH₂- or -O-;

----- represents a single bond or double bond;

Y¹ is N, C or CH;

Y² and Y³ are each independently N, CH₂ or CH, and Y² and Y³ are not both N at the same time;

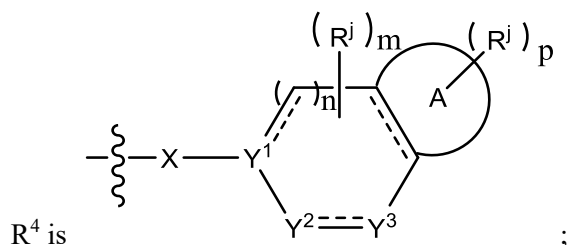
- 5 each R^j is independently -H, halogen, -OH, -NH₂, -CN, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkyl or -(C₁-C₆)alkoxy substituted by any number of halogen, oxazolyl, thiazolyl or triazolyl;

m and p are independently selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

- 10 ring A is furan, thiophene, oxazole, thiazole, triazole, piperidine, pyridine, pyran, thiopyran, morpholine, 1,4-dioxane, piperazine, pyrazine, or triazine.

In some of the second kind of embodiments,



X is a chemical bond, -CH₂-, -CH₂CH₂-, -NHCH₂-, -NHCH₂CH₂- or -O-;

----- represents a single bond or double bond;

- 15 Y¹ is N, C or CH;

Y² and Y³ are each independently N, CH₂ or CH, and Y² and Y³ are not both N at the same time;

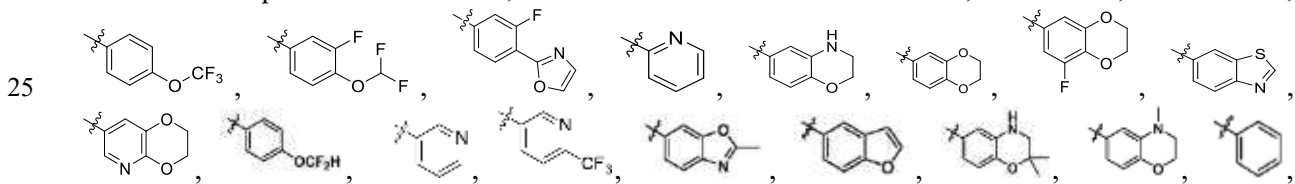
each R^j is independently -H, halogen, -OH, -NH₂, -CN, =O, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkyl substituted by any number of halogen, -(C₁-C₆)alkoxy substituted by any number of halogen, oxazolyl, thiazolyl, or triazolyl;

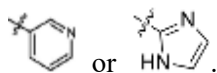
- 20 m and p are independently selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

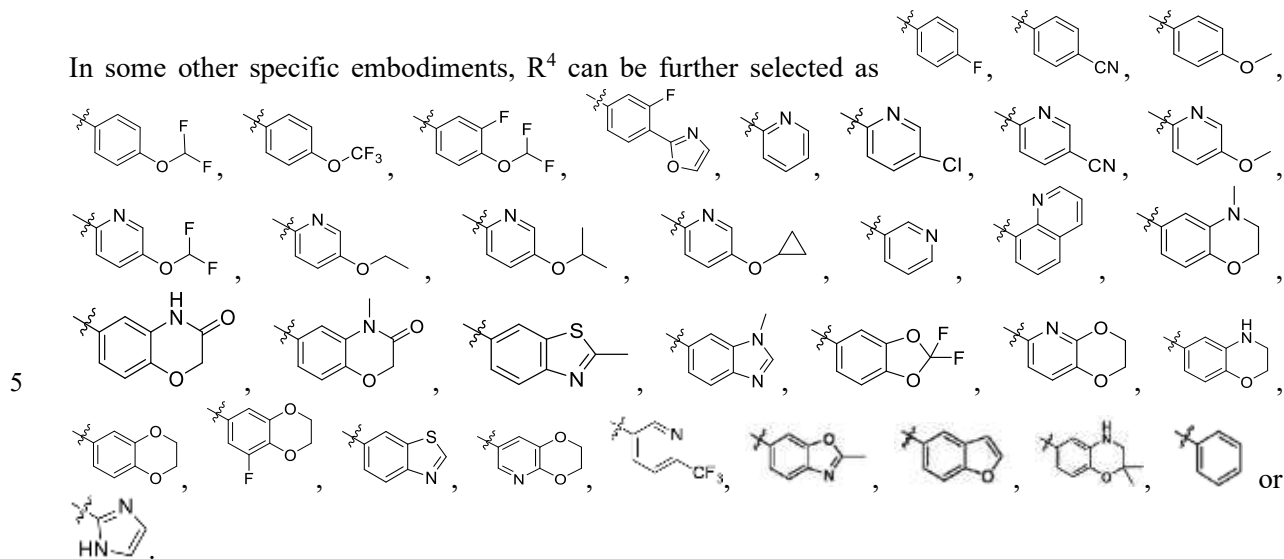
ring A is furan, thiophene, oxazole, thiazole, triazole, piperidine, pyridine, pyran, thiopyran, morpholine, 1,4-dioxane, piperazine, pyrazine, triazine, 4,5-dihydro-1H-imidazole, or 1,3-dioxolane.

In some other specific embodiments, R⁴ can be further selected as

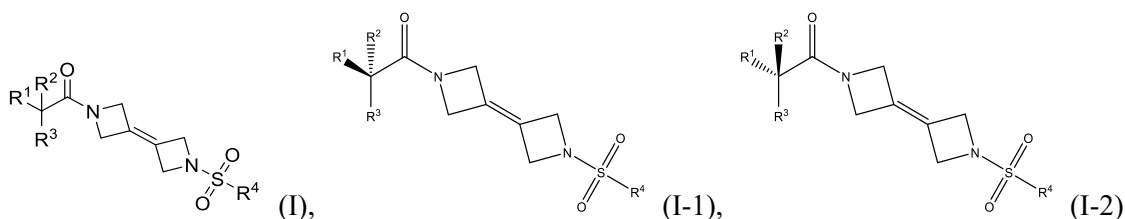




In some other specific embodiments, R⁴ can be further selected as



10 As the first one of the preferred options, in some embodiments, the compound of the present disclosure according to the first aspect, second aspect, third aspect and fourth aspect of the present disclosure is selected from a compound of formula I, I-1 or I-2, or an isomer, pharmaceutically acceptable salt or solvate thereof:



wherein,

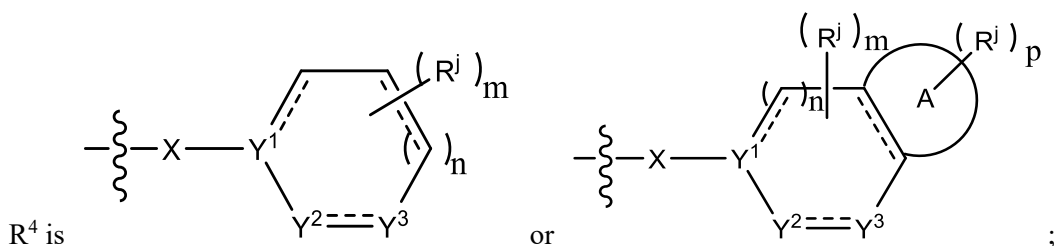
15 R¹ and R² are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆) linear alkyl, -(C₁-C₆) branched alkyl, -(C₃-C₆)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a, -OR^b, and -NR^cR^d;

20 or, R¹ and R² together with atoms to which they are attached can optionally bind to form -(C₃-C₈)cycloalkyl or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

25 R³ is -H, -F, -Cl, -Br, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, -(C₆-C₈) aryl, or 7-14 membered bicyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, aryl or fused ring group is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a and -OR^b;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is

optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, and -(C₁-C₆)alkyl;



X is a chemical bond, -CH₂-, -CH₂CH₂-, -NHCH₂-, -NHCH₂CH₂- or -O-;

5 ----- represents a single bond or double bond;

Y¹ is N, C or CH;

Y² and Y³ are each independently N, CH₂ or CH, and Y² and Y³ are not both N at the same time;

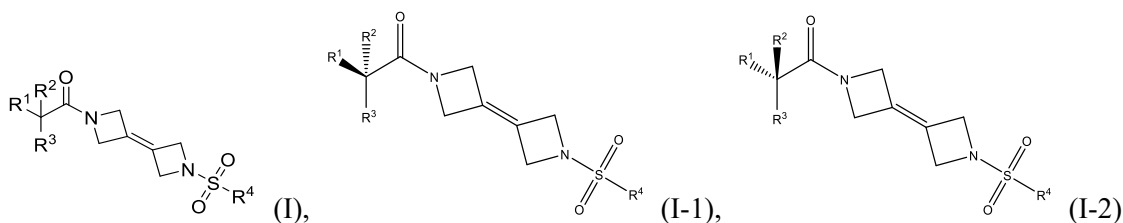
each R^j is independently -H, halogen, -OH, -NH₂, -CN, -(C₁-C₆)alkyl, -O-(C₁-C₆)alkyl, -(C₁-C₆)alkyl substituted by any number of halogen, -O-(C₁-C₆)alkyl substituted by any number of halogen, oxazolyl, thiazolyl or triazolyl; or, each R^j can be further independently selected from =O, -(C₃-C₆)cycloalkyl, -O-(C₃-C₆)cycloalkyl, -(C₃-C₆)cycloalkyl substituted by any number of halogen, and -O-(C₃-C₆)cycloalkyl substituted by any number of halogen;

m and p are independently 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

15 ring A is furan, thiophene, oxazole, thiazole, triazole, piperidine, pyridine, pyran, thiopyran, morpholine, 1,4-dioxane, piperazine, pyrazine or triazine; or, the ring A is 4,5-dihydro-1H-imidazole or 1,3-dioxolane.

As the second one of the preferred options, in some embodiments, the compound of the present disclosure according to the first aspect, second aspect, third aspect and fourth aspect of the present disclosure is selected from a compound of formula I, I-1 or I-2, or an isomer, pharmaceutically acceptable salt or solvate thereof:



wherein,

R² is -H, -F, -Cl or -Br;

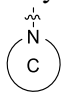
25 R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, -(CH₂)_qCH₃, -(CH₂)_qOH, -CH(OH)(CH₂)_qCH₃, -C(OH)((CH₂)_qCH₃)₂, HO-CH₂-, -(CH₂)_qNH₂, -(CH₂)_qNH(CH₂)_qCH₃, -(CH₂)_qN((CH₂)_qCH₃)₂, 3-6 membered heterocycloalkyl containing 1 N atom, or -(C₁-C₆)alkyl substituted by 3-6 membered heterocycloalkyl containing 1 N atom; or, R¹ is HO-CH₂-, -CH₂F, -CHF₂, -(CH₂)_qCH₂F, -(CH₂)_qCHF₂, -CH₂Cl, -CHCl₂, -(CH₂)_qCH₂Cl or

$-(CH_2)_qCHCl_2$;

q at each occurrence is independently 0, 1, 2, 3 or 4;

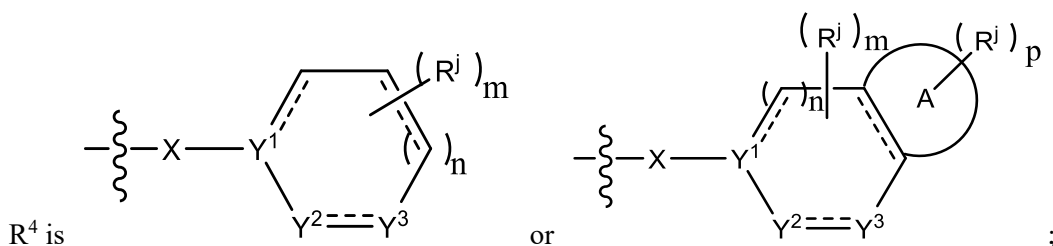
or, R^1 and R^2 together with atoms to which they are attached may optionally bind to form a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, tetrahydrofuran, tetrahydropyran, morpholine, dioxane or 2,3-dihydrobenzofuran ring; or, R^1 and R^2 together with the

atoms to which they are attached may optionally bind to form tetrahydro-2H-pyran or oxetane.
 R^3 is -H, -F, -Cl, -Br, $-(C_1-C_6)$ alkyl, $-(C_3-C_6)$ cycloalkyl, pyridyl, phenyl, benzothiazolyl, benzomorpholinyl or benzopyrrolidinyl, wherein the pyridyl, phenyl, benzothiazolyl, benzomorpholinyl, or benzopyrrolidinyl is optionally substituted by one or more substituents selected

from: -F, -Cl, -Br, $-(C_1-C_6)$ alkyl, $-(C_3-C_6)$ cycloalkyl, $-O-(C_1-C_6)$ alkyl, $-O-(C_3-C_6)$ cycloalkyl, piperazinyl, and piperazinyl substituted by any number of halogen or $-(C_1-C_6)$ alkyl; or, R^3 is ,

wherein ring  is a 3-6 membered saturated or unsaturated N-containing heterocyclyl connected through an N atom, in addition to the N atom, the heterocyclyl optionally contains 1-2 heteroatoms

independently selected from O, N and S, and  is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, $-(C_1-C_6)$ alkyl, $-(C_3-C_6)$ cycloalkyl, $-O-(C_1-C_6)$ alkyl, $-O-(C_3-C_6)$ cycloalkyl, $-(C_1-C_6)$ haloalkyl, $-(C_3-C_6)$ halocycloalkyl, $-O-(C_1-C_6)$ haloalkyl, $-O-(C_3-C_6)$ halocycloalkyl, pyrazolyl, pyrazolyl substituted by any number of halogen or $-(C_1-C_6)$ alkyl, piperazinyl, piperazinyl substituted by any number of halogen or $-(C_1-C_6)$ alkyl.



X is a chemical bond, $-CH_2-$, $-CH_2CH_2-$, $-NHCH_2-$, $-NHCH_2CH_2-$ or $-O-$;

===== represents a single bond or double bond;

Y^1 is N, C or CH;

Y^2 and Y^3 are each independently N, CH_2 or CH, and Y^2 and Y^3 are not both N at the same time;

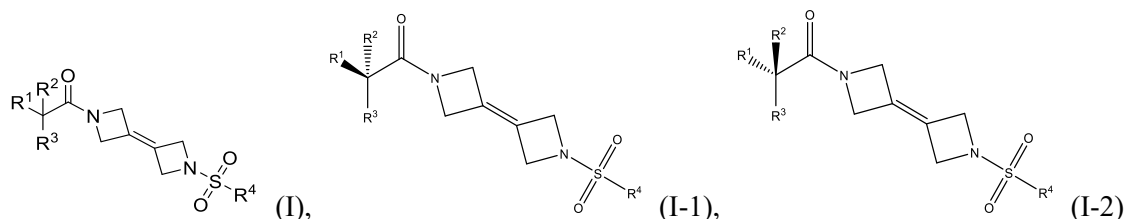
each R^j is independently -H, halogen, -OH, $-NH_2$, -CN, $-(C_1-C_6)$ alkyl, $-O-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkyl substituted by any number of halogen, $-O-(C_1-C_6)$ alkyl substituted by any number of halogen, oxazolyl, thiazolyl or triazolyl; alternatively, each R^j can be further independently selected from =O, (C_3-C_6) cycloalkyl, $-O-(C_3-C_6)$ cycloalkyl, $-(C_3-C_6)$ cycloalkyl substituted by any number of halogen, or $-O-(C_3-C_6)$ cycloalkyl substituted by any number of halogen;

m and p are independently 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

ring A is furan, thiophene, oxazole, thiazole, triazole, piperidine, pyridine, pyran, thiopyran, morpholine, 1,4-dioxane, piperazine, pyrazine or triazine; or, the ring A is 4,5-dihydro-1H-imidazole or 1,3-dioxolane.

- As the third one of the preferred options, in some embodiments, the compound of the present disclosure according to the first aspect, second aspect, third aspect and fourth aspect of the present disclosure is selected from a compound of formula I, I-1 or I-2, or an isomer, pharmaceutically acceptable salt or solvate thereof:



wherein,

- R^2 is -H, -F, -Cl or -Br;

R^1 is -H, -F, -Cl, -Br, -OH, -NH₂, HO-CH₂-, HO-CH₂CH₂-, HO-CH₂CH₂CH₂-, HO-CH₂CH₂CH₂CH₂-, NH-CH₂-, NH-CH₂CH₂-, NH-CH₂CH₂CH₂-, or ; alternatively, R^1 is HO-CH₂-, F-CH₂- or .

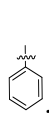
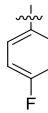
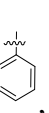
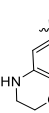
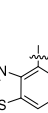
alternatively, R^1 and R^2 together with the atoms to which they are attached may optionally bind to form

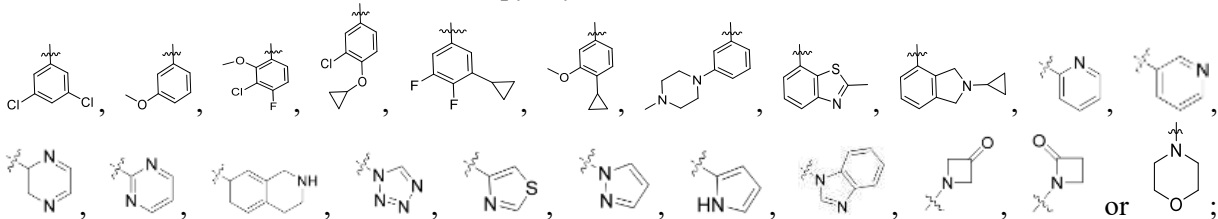


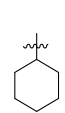
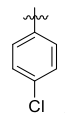
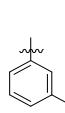
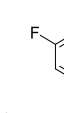
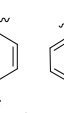
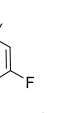
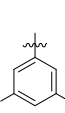
; or, R^1 and R^2 together with the atoms to which they are attached may optionally bind to form

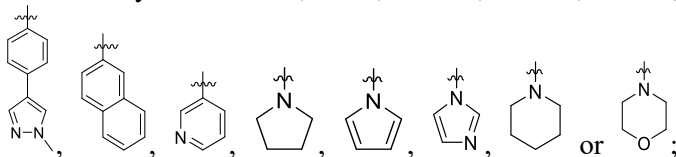


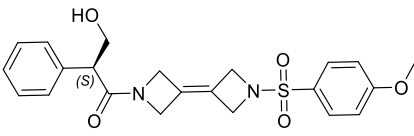
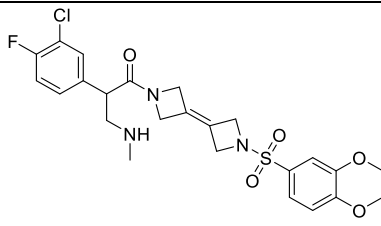
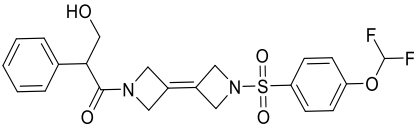
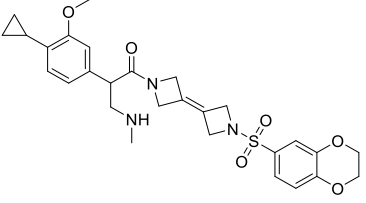
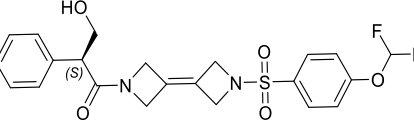
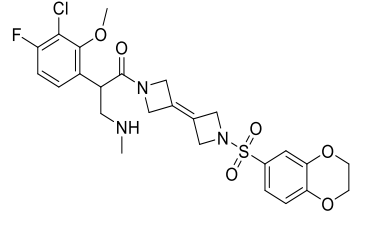
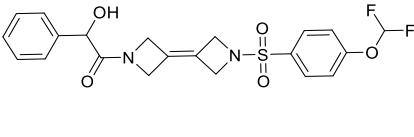
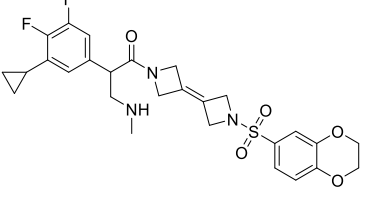
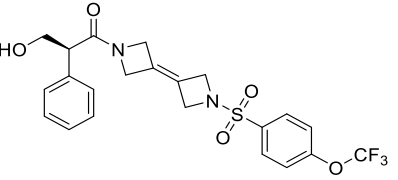
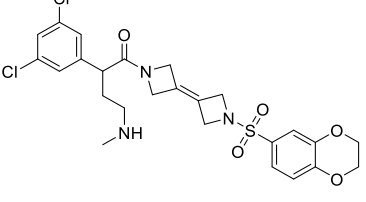
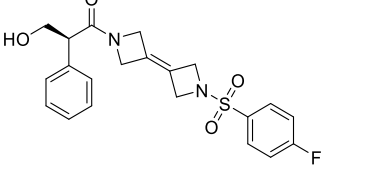
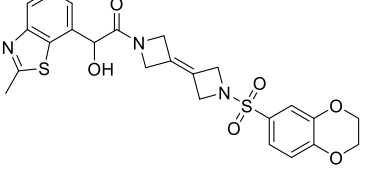
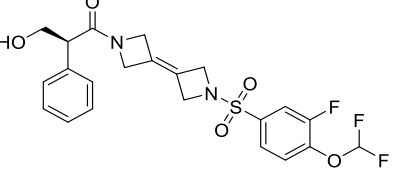
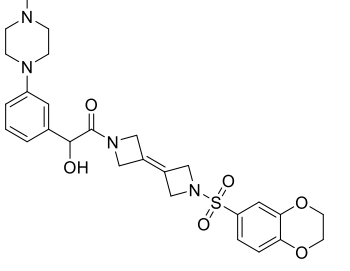
or .

R^3 is -H, -F, -Cl, -Br, -CH₃, -CH₂CH₃, pyridyl, , , F, , , , Cl, , ,



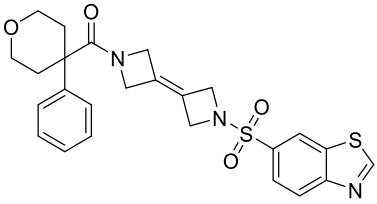
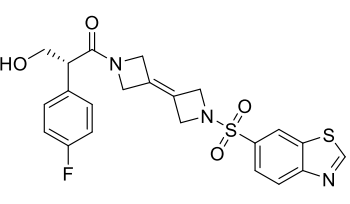
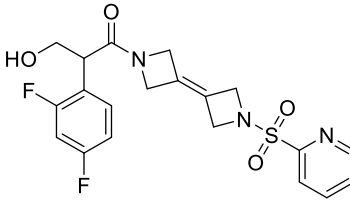
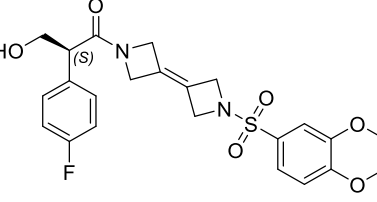
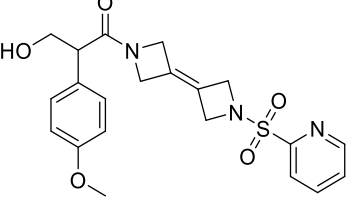
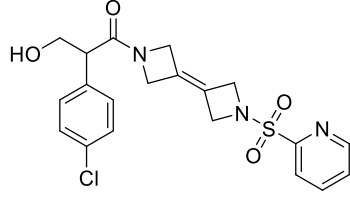
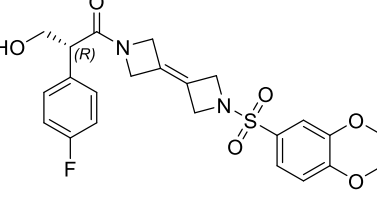
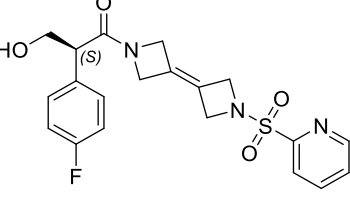
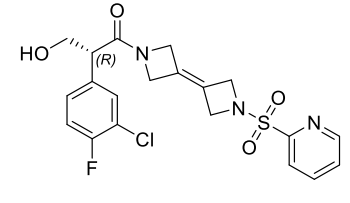
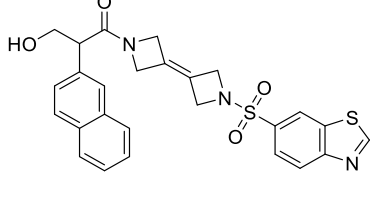
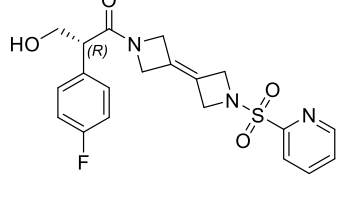
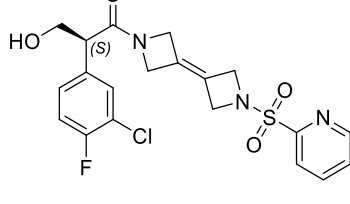
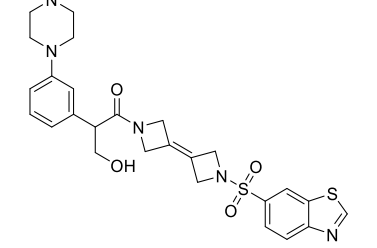
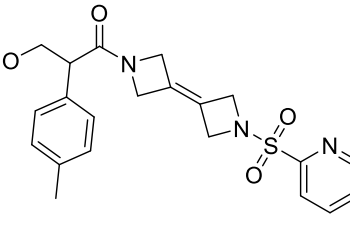
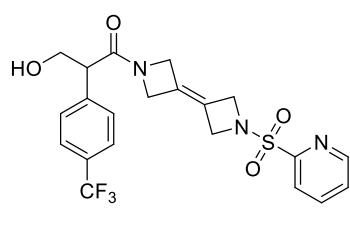
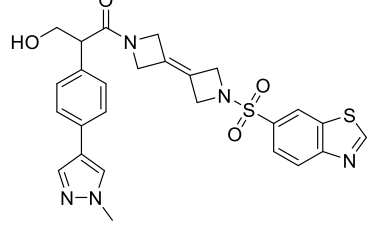
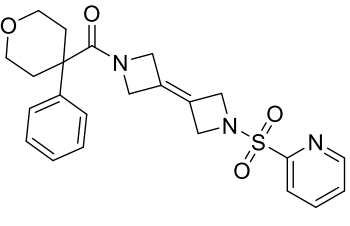
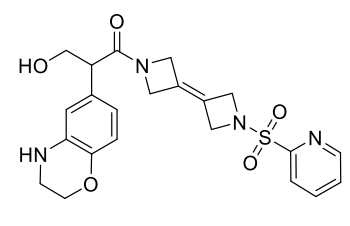
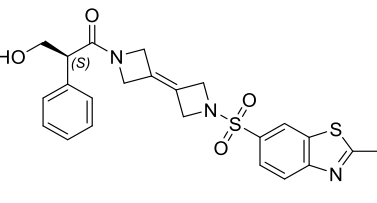
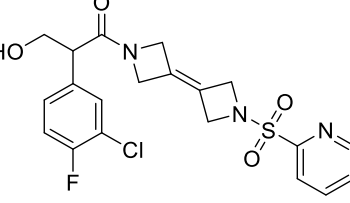
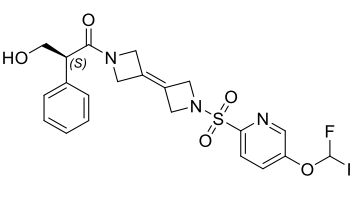
alternatively R^3 is , Cl, , F, , F, , CN, , , CF₃, ,



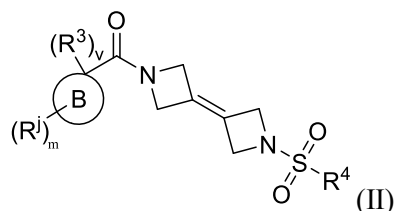
	
	
	
	
	
	
	

Preferably, the compound of the present disclosure used in the first, second, third and fourth aspects of the present disclosure is selected from the compounds shown in the following table, or isomers, pharmaceutically acceptable salts or solvates thereof:

5 Preferably, the compound of the present disclosure according to the first aspect, second aspect, third aspect and fourth aspect of the present disclosure is selected from the compounds shown in the following table, or isomers, pharmaceutically acceptable salts or solvates thereof:

In another embodiment, the compound of the present disclosure according to the first, second, third and fourth aspects of the present disclosure is selected from a compound of formula II, or an isomer, pharmaceutically acceptable salt or solvate thereof:



5 in the formula II:

R^3 and R^4 are defined as any corresponding R^3 and R^4 of the aforementioned compound of formula I, I-1 or I-2;

each R^i is independently -H, halogen, -OH, -NH₂, -CN, =O, -NO₂, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered
 10 heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH, -C(O)H or -C(O)OH, wherein each of the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more
 15 substituents selected from: -H, =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH or -NHS(O)OH, -C(O)H, -C(O)OH, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, or 5-14 membered heteroaryl containing 1-4 heteroatoms independently
 20 selected from O, N and S;

m is independently an integer selected from 0, 1, 2, 3, 4, 5 or 6;

v is 0 or 1;

ring B is (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl
 25 containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S.

In some other specific embodiments,

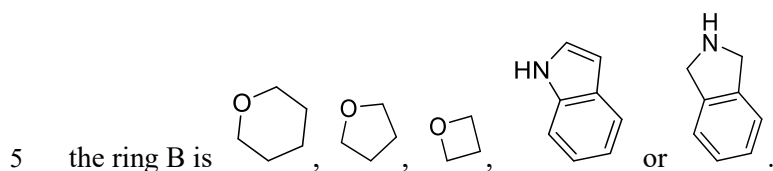
each R^i is independently -H, halogen, -OH, -NH₂, -CN, =O, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkyl substituted by any number of halogen, -(C₁-C₆)alkoxy substituted by any number of
 30 halogen, oxazolyl, thiazolyl, and triazolyl;

the ring B is (C₃-C₈)cycloalkyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered bicyclic or tricyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S.

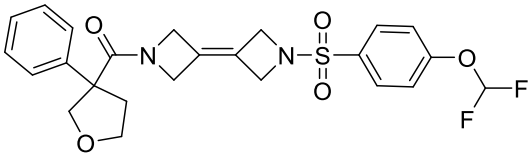
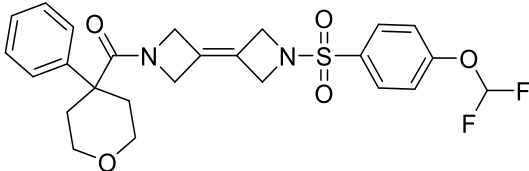
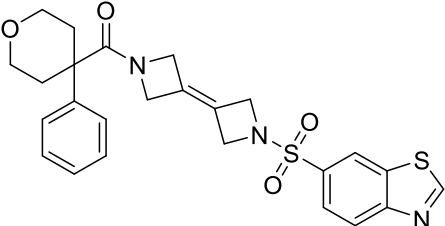
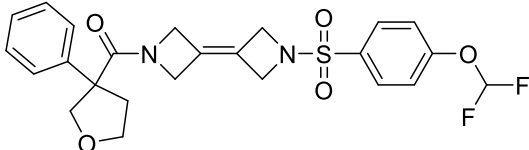
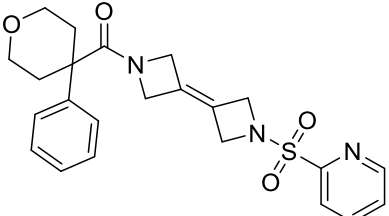
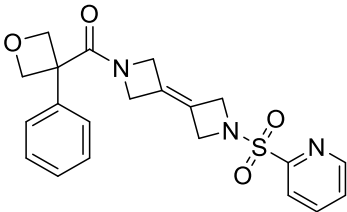
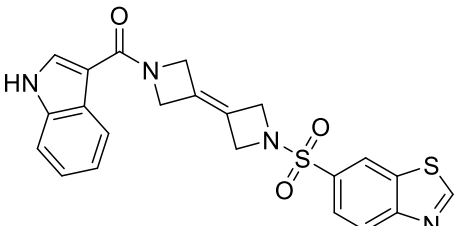
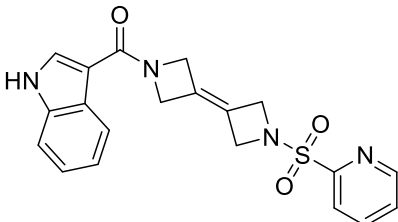
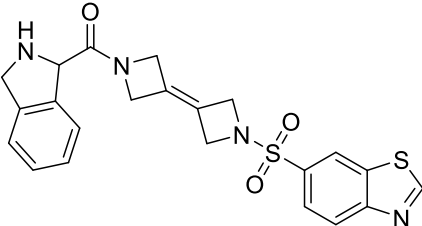
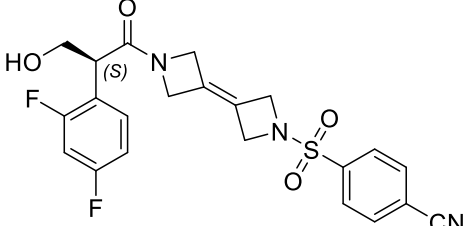
35 In some other specific embodiments,

the ring B is 3-7 membered oxacycloalkyl or 8-10 membered azabicyclic fused heteroaryl. Alternatively, the ring B is oxacycloheptane, oxacyclohexane, tetrahydrofuran, oxetane, oxacyclopropane, 1H-indole or isoindoline.

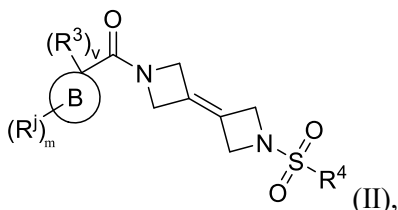
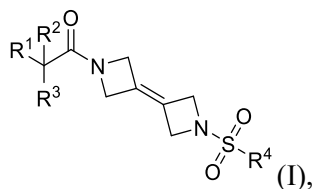
In some other specific embodiments,



Preferably, the compound of the present disclosure according to the first, second, third and fourth aspects of the present disclosure is selected from the compounds shown in the following table, or isomers, pharmaceutically acceptable salts or solvates thereof:

In another embodiment, the compound of the present disclosure according to the first, second, third and fourth aspects of the present disclosure is selected from a deuterated compound of the aforementioned formula I or II, or an isomer, pharmaceutically acceptable salt or solvate thereof:

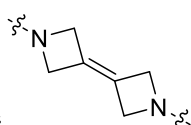


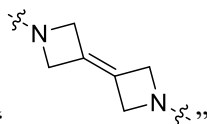
5

wherein, R^1 , R^2 , R^3 , R^4 , R^j , m , v and the ring B are defined as any corresponding R^1 , R^2 , R^3 , R^4 , R^j , m , v and ring B in the aforementioned compound of formula I or II;

any one or more H in the compound of formula I or II are substituted by D.

In some other specific embodiments,

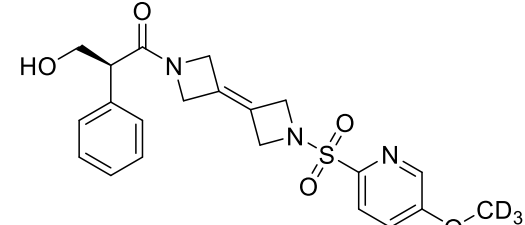
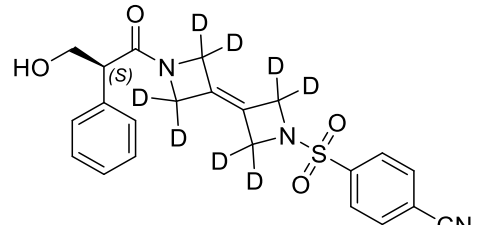
- 10 in the compound of formula I or II, any one or more H in the structure “” are substituted by D, or any one or more H in R^4 are substituted by D. Alternatively, in the compound of

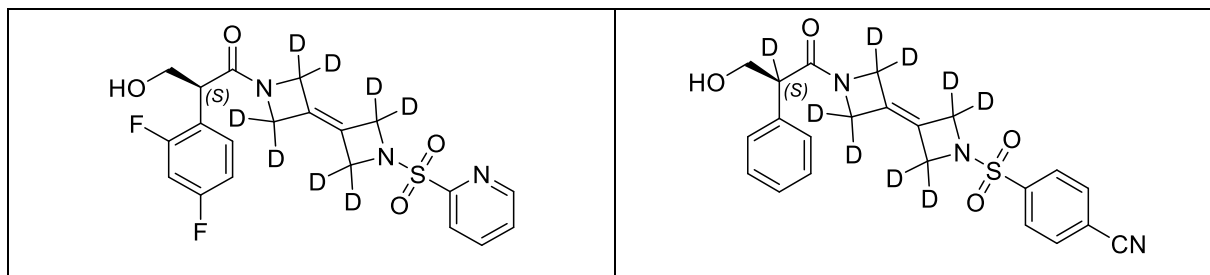
formula I or II, all H in the structure “” are substituted by D.

In some other specific embodiments,

R^1 , R^2 or R^3 is independently and optionally substituted by D when being selected as H.

- 15 Preferably, the compound of the invention according to the first, second, third and fourth aspects of the invention is selected from the compounds shown in the following table, or isomers, pharmaceutically acceptable salts or solvates thereof:

	
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In one embodiment, the content of the compound of the present disclosure in the pharmaceutical composition according to the first, second, third and fourth aspects of the present disclosure is 0.05 mg to 1000 mg, and in particular, the content of the compound of the present disclosure in the unit dose of the pharmaceutical composition is 0.05 mg to 1000 mg, wherein the unit dose refers to the minimum metering unit specification product of the pharmaceutical composition or the drug prepared from the pharmaceutical composition.

In some embodiments, the pharmaceutical composition comprising the compound of the present disclosure can be presented in any pharmaceutically acceptable dosage form and route of administration. Acceptable dosage forms include, but are not limited to, tablets, capsules, granules, pills, pastes, powder, tinctures, films, patches, liniment, implants, injections, lozenges, drops, sprays, aerosols, nebulized inhalers, gels, suppositories, ointments, etc. Acceptable routes of administration include, but are not limited to, oral, intravenous, rectal, parenteral, topical, transdermal, ocular, nasal, buccal or pulmonary (inhalation) administration, etc.

In the present disclosure, when a later technical solution further defines a previous technical solution, it may only further define some of the technical features. In this case, the undefined technical features may be optionally defined in the previous technical solution or anywhere in the present disclosure.

Definition

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

“Alkyl” refers to an aliphatic hydrocarbon group, and refers to a saturated hydrocarbon group, which may be substituted or unsubstituted. The alkyl moiety may be a linear or branched alkyl. For example, it is $-(C_1-C_6)$ alkyl or $-(C_1-C_3)$ alkyl. The $-(C_1-C_6)$ alkyl refers to an alkyl with 1 to 6 carbon atoms, for example an alkyl with 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms. Non-limiting examples of the alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, and the like. The alkyl may be unsubstituted or substituted by one or more substituents, including but not limited to alkyl, alkoxy, cyano, hydroxyl, carbonyl, carboxyl, aryl, heteroaryl, amido, halogen, sulfonyl, sulfinyl, phosphonyl, etc.

“Alkenyl” refers to an unsaturated hydrocarbonyl containing a carbon-carbon double bond in its structure, which may be substituted or unsubstituted. The alkenyl moiety may be a linear or branched alkenyl. For example, it is $-(C_2-C_6)$ alkenyl or $-(C_2-C_4)$ alkenyl. $-(C_2-C_6)$ alkenyl refers to an alkenyl with 2 to 6 carbon atoms, for example an alkenyl with 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms. Non-limiting examples of the alkenyl include vinyl, n-propenyl, isopropenyl, n-butenyl, isobutenyl, n-hexenyl, and the like. The alkenyl may be unsubstituted or substituted by one or more substituents, including but not limited to alkyl, alkoxy, cyano, hydroxyl, carbonyl, carboxyl,

aryl, heteroaryl, amido, halogen, sulfonyl, sulfinyl, phosphoryl, etc.

“Alkynyl” refers to an unsaturated hydrocarbonyl containing a carbon-carbon triple bond in its structure, which may be substituted or unsubstituted. The alkynyl moiety may be a linear or branched alkynyl. For example, it is $-(C_2-C_6)$ alkynyl or $-(C_2-C_4)$ alkynyl. $-(C_2-C_6)$ alkynyl refers to an alkynyl with 2 to 6 carbon atoms, for example an alkynyl with 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms. Non-limiting examples of the alkynyl include ethynyl, n-propynyl, isopropynyl, n-butylnyl, isobutylnyl, n-hexynyl, and the like. The alkynyl may be unsubstituted or substituted by one or more substituents, including but not limited to alkyl, alkoxy, cyano, hydroxyl, carbonyl, carboxyl, aryl, heteroaryl, amido, halogen, sulfonyl, sulfinyl, phosphoryl, etc.

“Ring” refers to any covalently closed structure, including, for example, a carbocycle (e.g., aryl, cycloalkyl, or cycloalkenyl), heterocyclyl (e.g., heteroaryl, heterocycloalkyl, or heterocycloalkenyl), an aromatic group (e.g., aryl or heteroaryl), and a non-aromatic group (e.g., cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl), which may be substituted or unsubstituted. The ring may be optionally substituted and may be monocyclic or polycyclic. Typical polycyclic rings generally include bicyclic rings and tricyclic rings. The ring of the present application usually has 3-20 ring atoms, for example 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 ring atoms.

The “membered” refers to the number of skeleton atoms constituting a ring. A typical 5-membered ring includes, for example, cyclopentyl, pyrrole, imidazole, thiazole, furan and thiophene, etc.; and a typical 6-membered ring includes, for example, cyclohexyl, cyclohexenyl, pyridine, pyran, pyrazine, thiopyran, pyridazine, pyrimidine, benzene, etc. A ring containing a heteroatom among skeleton atoms is a heterocyclic ring.

“Heteroatom” refers to an atom other than carbon or hydrogen. One or more heteroatoms in the heterocycle of the present application can be independently selected from O, S, N, Si and P, but are not limited thereto.

An “aromatic group” refers to a cyclic group with a conjugated π electron system, including an aryl in which the skeleton atoms constituting the ring are all carbon atoms and a heteroaryl in which the skeleton atoms constituting the ring contain a heteroatom. “Aryl” preferably refers to a monocyclic or fused polycyclic (i.e., rings sharing pairs of adjacent carbon atoms) group of 6 to 14 carbon atoms (6 to 14 membered) having a conjugated π electron system, preferably having 6 to 10 atoms, such as phenyl and naphthyl, which may be substituted or unsubstituted. More preferred is phenyl. “Heteroaryl” preferably refers to a heteroaromatic system containing 1 to 4 (e.g. 1, 2, 3 or 4) heteroatoms, and 5 to 14 (e.g. 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14) ring atoms, wherein the heteroatom is selected from oxygen, sulfur and nitrogen, and the heteroaryl may be substituted or unsubstituted. The heteroaryl preferably is 5 to 10 membered and contains 1 to 3 heteroatoms; more preferably is 5 or 6 membered and contains 1 to 2 heteroatoms; and preferably, for example, imidazolyl, furanyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, pyrrolyl, triazolyl, tetrazolyl, pyridinyl, pyranyl, thiopyranyl, pyrimidinyl, thiadiazole, pyrazinyl, triazinyl, etc., preferably imidazolyl, thiazolyl, pyrazolyl or pyrimidinyl, thiazolyl; and more preferably pyrazolyl such as 1H-pyrazol-4-yl or thiazolyl. The heteroaryl ring can be fused to an aryl, heterocycloalkyl, cycloalkyl ring, or another heteroaryl to form a fused heteroaryl. The fused heteroaryl is preferably an 8-10 membered fused heteroaryl, including but not limited to: indolyl for example 1H-indol-5-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazolyl for example 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl, or 1H-benzo[d]imidazolyl for example

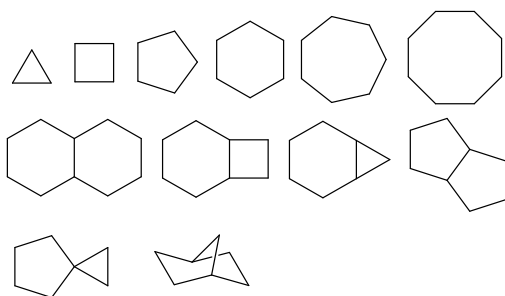
1H-benzo[d]imidazol-6-yl.

A “non-aromatic group” refers to a cyclic group that does not have a conjugated π electron system and is not aromatic. It is also generally called an alicyclic group, i.e., an alicyclic radical, including a cycloalkyl or cycloalkenyl in which skeleton atoms constituting the ring are all carbon atoms, and heterocycloalkyl or heterocycloalkenyl in which skeleton atoms constituting the ring contain heteroatoms.

The “fused” refers to rings that share adjacent pairs of carbon atoms, and typically is bicyclic or tricyclic fused.

A “fused ring group” includes a “fused non-aromatic group” and a “fused aromatic group”, wherein the “fused non-aromatic group” includes a “fused cycloalkyl”, a “fused heterocycloalkyl”, a “fused cycloalkenyl” and a “fused heterocycloalkenyl”, and the “fused aromatic group” includes a “fused aryl” and a “fused heteroaryl”, which may be all substituted or unsubstituted.

The “cycloalkyl” refers to a saturated cyclic hydrocarbon substituent containing 1-3 rings, including monocycloalkyl, bicycloalkyl and tricycloalkyl, which contains 3-20 carbon atoms that can form a ring, preferably 3-10 carbon atoms (i.e., 3-10 membered cycloalkyl, also known as $-(C_3-C_{10})$ cycloalkyl), e.g., 3 to 8, 3 to 7, 3 to 6, 5 to 6 carbon atoms. Preferably, the cycloalkyl is selected from a monovalent cycloalkyl derived from the following rings:

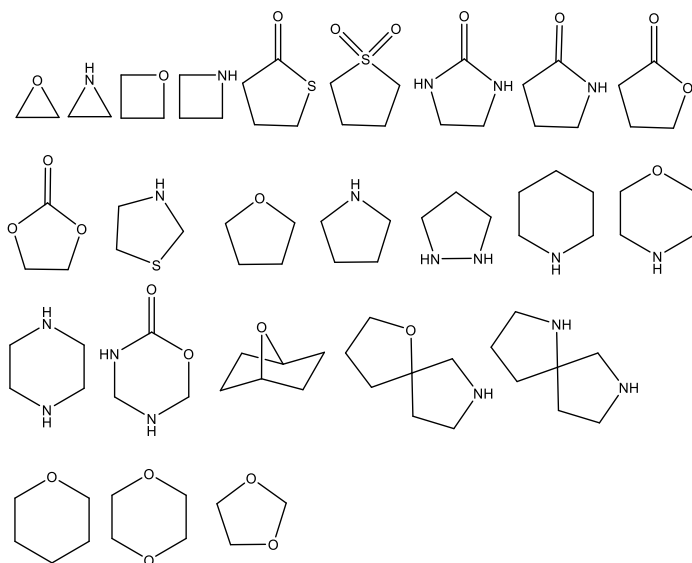


, preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. The cycloalkyl may be substituted or unsubstituted.

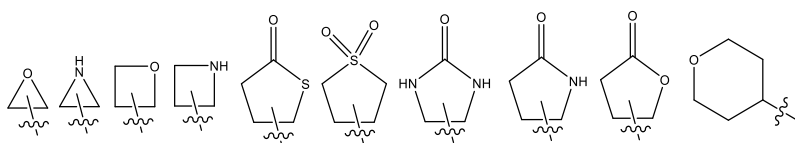
It should be understood that when a cycloalkyl is linked to two groups according to a structure or context, the cycloalkyl is a divalent group, i.e., having two linking sites. At this time, it may also be named as a cycloalkylene group. Examples of preferred cycloalkylene groups include, but are not limited to, monocyclic structures, such as cyclopropylene, cyclobutylene, cyclopentylene (e.g. cyclopent-1,2-diyl, cyclopent-1, 3-diyl), cyclohexylene (e.g. cyclohex-1,2-diyl, cyclohex-1,3-diyl, cyclohex-1,4-diyl), cycloheptylene or cyclooctylene, etc.

“Heterocycloalkyl” and “cycloheteroalkyl” are used interchangeably and refer to a saturated and nonaromatic monocyclic ring, fused ring, bridged ring or spiro ring containing one or more (e.g., 1, 2,

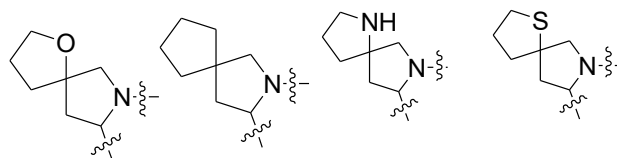
3, or 4) heteroatoms. The heteroatom may be N, O, S or SO_2 () , and preferably N, O and/or S. The heterocycloalkyl may be a 3 to 10 membered (e.g., 3, 4, 5, 6, 7, 8, 9, or 10 membered, i.e., including 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms) monocyclic, bicyclic or tricyclic group. A typical heterocycloalkyl includes, but is not limited to, monovalent groups derived from the following rings:



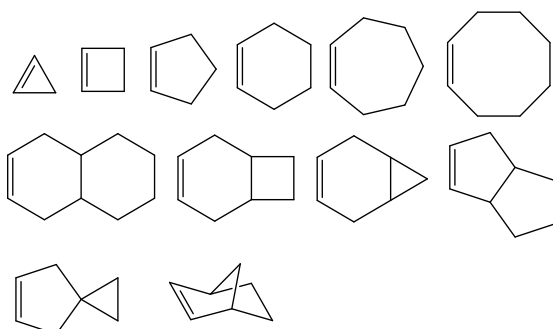
. These heterocycloalkyl groups can also be represented by commonly understood structural formulae, for example:



It should be understood that when a heterocycloalkyl is linked to two groups according to a structure or context, the heterocycloalkyl is a divalent group, i.e., having two linking sites. At this time, it may also be named as a heterocycloalkylene group. Examples of the heterocycloalkylene group include, but are not limited to, divalent groups formed from the aforementioned groups, for example:



“Cycloalkenyl” refers to a cyclic hydrocarbon substituent including 1-3 rings, which contains one or more double bonds, but no ring of which has a completely conjugated π electron system and which is not aromatic, including monocycloalkenyl, bicyclicalkenyl and tricyclicalkenyl, which contain 3-20 carbon atoms that can form a ring, preferably 3-10 carbon atoms (i.e., 3-10 membered cycloalkenyl, also known as $-(C_3-C_{10})$ cycloalkenyl), for example, 3 to 8, 3 to 7, 3 to 6, or 5 to 6 carbon atoms. Preferably, the cycloalkenyl is selected from a monovalent cycloalkenyl derived from the following rings:

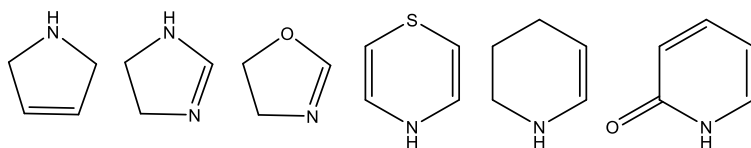


, preferably cyclopropenyl, cyclopentenyl, and

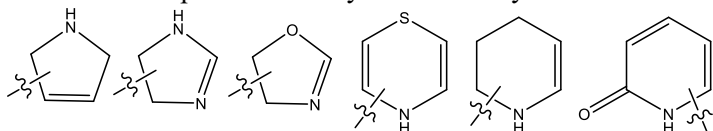
cyclohexenyl. The cycloalkenyl may be substituted or unsubstituted. It should be understood that when a cycloalkenyl is linked to two groups according to a structure or context, the cycloalkenyl is a divalent group, i.e., having two linking sites. At this time, it may also be named as a cycloalkenylene group.

“Heterocycloalkenyl” refers to an unsaturated and nonaromatic monocyclic ring, fused ring, bridged ring or spiro ring containing one or more (e.g., 1, 2, 3, or 4) heteroatoms. The heteroatom may be N, O,

S or SO₂ () , and preferably N, O and/or S. The heterocycloalkenyl can be a 3 to 10 membered (e.g., 3, 4, 5, 6, 7, 8, 9, or 10 membered, i.e., including 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms) monocyclic, bicyclic or tricyclic group. Typical heterocycloalkenyl groups include, but are not limited to, monovalent groups derived from the following rings:



. These heterocycloalkenyl groups can also be represented by commonly understood structural formulae, for example:



. It should be understood that when a heterocycloalkenyl is linked to two groups according to a structure or context, the heterocycloalkenyl is a divalent group, i.e., having two linking sites. At this time, it may also be named as a heterocycloalkenylene group.

“Oxo” refers to that a hydrogen on the carbon is replaced by =O.

“Halogen” or “halo” refers to fluorine, chlorine, bromine or iodine.

“Haloalkyl” refers to an alkyl in which at least one hydrogen is replaced by a halogen atom, for example CF₃.

The “substituted” means that one or more hydrogen atoms, preferably up to 5 (e.g., 1, 2, 3, 4, or 5), more preferably 1-3 hydrogen atoms in a group can be independently substituted by corresponding number of substituents from each other. It goes without saying that, the substituents are only in their possible chemical positions, and those of skills in the art are able to determine (either experimentally or theoretically) possible or impossible substitutions without undue effort. For example, an amino or hydroxyl group with a free hydrogen may be unstable when binds with a carbon atom with an unsaturated (e.g. olefinic) bond.

“Inhibitor” refers to a substance that reduces enzyme activity.

“Agonist” refers to a substance that increases enzyme activity.

“Optionally” means that the subsequently described event or environment can but not necessarily occur, indicating that the event or environment occurs or doesn’t occur.

The term “substituted or unsubstituted” in the present disclosure means that any group is mono- or poly-substituted by a specified substituent to the extent that such mono- or poly-substitution (including multiple substitutions on the same moiety) is chemically permissible, wherein each substituent may be

located at any available position on the group and may be linked through any available atom on the substituent. "Any available position" refers to any position on a group that is chemically accessible by methods known in the art or methods taught in the present disclosure and does not produce an unduly unstable molecule. When there are two or more substituents on any group, each substituent is defined independently of any other substituent and therefore may be the same or different.

As for "stereoisomerism", the "stereoisomer" described in the present disclosure refers to that when a compound of the present disclosure contains one or more asymmetric centers, the compound can be existed in forms of racemates, racemic mixtures, single enantiomer, diastereomeric mixtures and single diastereoisomer. The compound of the present disclosure may have an asymmetric center, and thus results in the presence of two optical isomers. The scope of the present disclosure encompasses all possible optical isomers and mixtures thereof. If the compound of the present disclosure contains an olefin double bond, the scope of the present disclosure includes *cis* and *trans* isomers, unless otherwise specified. The compound of the present disclosure may be existed in forms of tautomers (one of functional group isomers) that have different linking sites of hydrogens through shifts of one or more double bonds. For example, a ketone and an enol form thereof are keto-enol tautomers. Each tautomer and mixtures thereof are within the scope of the present disclosure. Enantiomers, diastereomers, racemates, mesomers, *cis-trans* isomers, tautomers, geometric isomers, epimers and mixtures of all compounds are all within the scope of the present disclosure.

The term "compound of the present disclosure" used in the present disclosure is intended to encompass compounds of general formulae (I) and (II) as defined in the present disclosure or any preferred or specific embodiment thereof (including compounds of formulae (I-1) and (I-2) and the like, and example compounds), and stereoisomers, pharmaceutically acceptable salts, tautomers or solvates thereof.

The term "pharmaceutically acceptable" used in the present disclosure means molecular entities and compositions that are approved by or approvable by respective authorities in various countries, or listed in a generally recognized pharmacopoeia for use in animals and more particularly human, or do not produce adverse, allergic or other adverse responses when being administered in appropriate amount to animals, such as human.

The term "pharmaceutically acceptable salt" used in the present disclosure means a salt of a compound of the present disclosure that is pharmaceutically acceptable and possesses the desired pharmacological activity of the parent compound. Specifically, such salts are non-toxic and can be inorganic or organic acid addition salts and alkali addition salts.

The term "individual" used in the present disclosure includes human or non-human animals. Exemplary human individuals include human individuals (referred to as patients) suffering from a disease (e.g., disease described in the present disclosure) or normal individuals. In the present disclosure, "non-human animals" include all vertebrates, e.g., non-mammals (e.g., birds, amphibians, reptiles) and mammals, e.g. non-human primates, livestock and/or domesticated animals (e.g., sheep, dogs, cats, cows, pigs, etc.).

"Pharmaceutical composition" mentioned in the present disclosure refers to a composition including one or more compounds of formula (I), formula (I-1), formula (I-2) or formula (II) or stereoisomers, tautomers, pharmaceutically acceptable salts or solvates thereof, and carriers or excipients generally

accepted in the art for delivering the biologically active compound to an organism (e.g., human).

The term "pharmaceutical combination" used in the present disclosure refers to that the compound of the present disclosure may be combined with other active agents for achieving the purposes of the present disclosure. The other active agents may be one or more additional compounds of the present disclosure, or may be a second or additional (e.g., a third) compound that is compatible with the compound of the present disclosure, i.e., does not adversely affect each other, or has complementary activity, such as Luspatercept (ACE-536), Ruxolitinib, Bitopertin (RO-4917838), hydroxyurea, IMR-687, Mitapivat (AG-348), etc. Such active agents are suitably present in combination in an amount effective to achieve the intended purpose. The other active agents may be co-administered with the compound of the present disclosure in a single pharmaceutical composition, or may be administered separately from the compound of the present disclosure in different discrete units, and may be administered simultaneously or sequentially when being administered separately. The sequential administrations may be close or distant in time.

It should be understood that when selecting each group in the structure of the compound of the present disclosure, the groups that have connection, coordination or influence with each other should be selected accordingly on the premise of complying with the rules of chemical valence bonding.

"Prevention" in the present disclosure refers to avoiding, alleviating, or reducing the risk of the occurrence and development of a disease; "treatment" refers to the use of artificial intervention to eliminate, hinder, alleviate, weaken, limit, inhibit or curb the symptoms of a disease or the development, process or progression of disease symptoms.

According to the content of the present disclosure, other modifications, substitutions or changes in various forms can also be made according to the common technical knowledge and means in the art, without departing from the aforementioned basic technical concept of the present disclosure.

DETAILED DESCRIPTION

In order to further illustrate the present disclosure, the active compounds of the present disclosure and preparation methods and use thereof are described in details hereafter in conjunction with examples.

The following abbreviations or terms have the following meanings:

Grubb's 2 represents a Grubbs second generation catalyst;

DMF represents N,N-dimethylformamide;

DMSO represents dimethyl sulfoxide;

HATU represents 2-(7-azabenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate;

DIPEA represents N,N-diisopropylethylamine;

Pd₂(dba)₃ represents tris(dibenzylideneacetone)dipalladium;

Xantphos represents 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene;

-Cbz represents a benzyloxycarbonyl protecting group;

-Boc represents a tert-butoxycarbonyl protecting group;

-Fmoc represents a 9-fluorenylmethoxycarbonyl protecting group;

-PMB represents a p-methoxybenzyl protecting group;

-Bn represents a benzyl protecting group;

-Trt represents a trityl protecting group;

5 -Tos represents a tosyl protecting group;

-Pht represents a phthalyl protecting group;

-Alloc represents an allyloxycarbonyl protecting group;

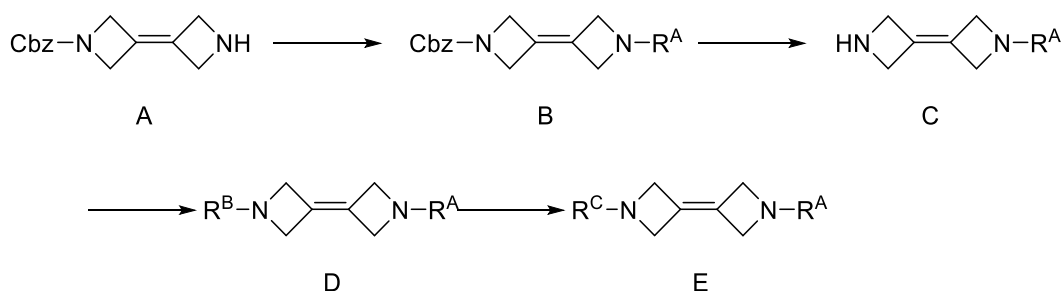
Tris buffer represents a tris(hydroxymethyl)aminomethane buffer;

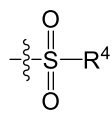
-TBS represents tert-butyldimethylsilyl;

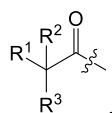
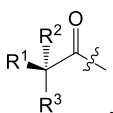
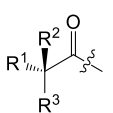
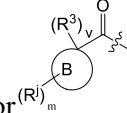
10 -TBDPS represents tert-butyldiphenylsilyl.

The present disclosure further provides a synthesis method of the compound of the present disclosure. The synthesis method of the present disclosure is mainly based on the preparation method reported in the chemical literatures or using commercially available chemical reagents as starting materials for related synthesis.

15 **Method:**



In the aforementioned reaction formula, “R^A” refers to , wherein R⁴ is as defined wherever it

appears in the present disclosure; “R^C” refers to , ,  or , wherein R¹, R², R³, R^j, m, v and ring B are as defined wherever they appear in the present disclosure; “R^B” refers to R^C protected by a protecting group, R^B becomes R^C after the protecting group is removed. The protecting group includes but is not limited to -TBS or -TBDPS.

The following steps involve a compound Z-R^A and a compound Z-R^B, wherein “Z” is a group capable of undergoing a condensation reaction with an amino group to connect R^A or R^B onto “-N-(1,2,3,4-tetrahydropyridine-2-ylidene)-1,2,3,4-tetrahydropyridine-5-amine-”, and the condensation reaction is preferably a condensation reaction between

25 sulfonyl chloride and an amino group or a condensation reaction between a carboxyl group and an amino group, “Z” can be independently selected implementing groups in different compounds, including but not limited to -Cl, -F, -Br, -OH. The compound Z-R^A is preferably Cl-R^A, and the

compound Z-R^B is preferably OH-R^B.

Step 1:

Compound A is dissolved in a tetrahydrofuran solution, then added with triethylamine and a compound Z-R^A to react at 25°C. After the reaction is completed, the product is extracted with ethyl acetate for three times, and the organic phases are combined, dried over anhydrous sodium sulfate, filtered, concentrated and then separated and purified through a chromatography column to obtain **compound B**.

Step 2:

The **compound B** is dissolved in trifluoroacetic acid to react at 60°C. After the reaction is completed, the product is concentrated to dryness and then separated and purified through a chromatography column to obtain **compound C**.

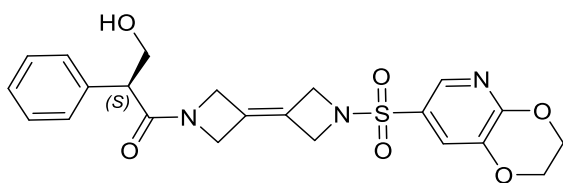
Step 3:

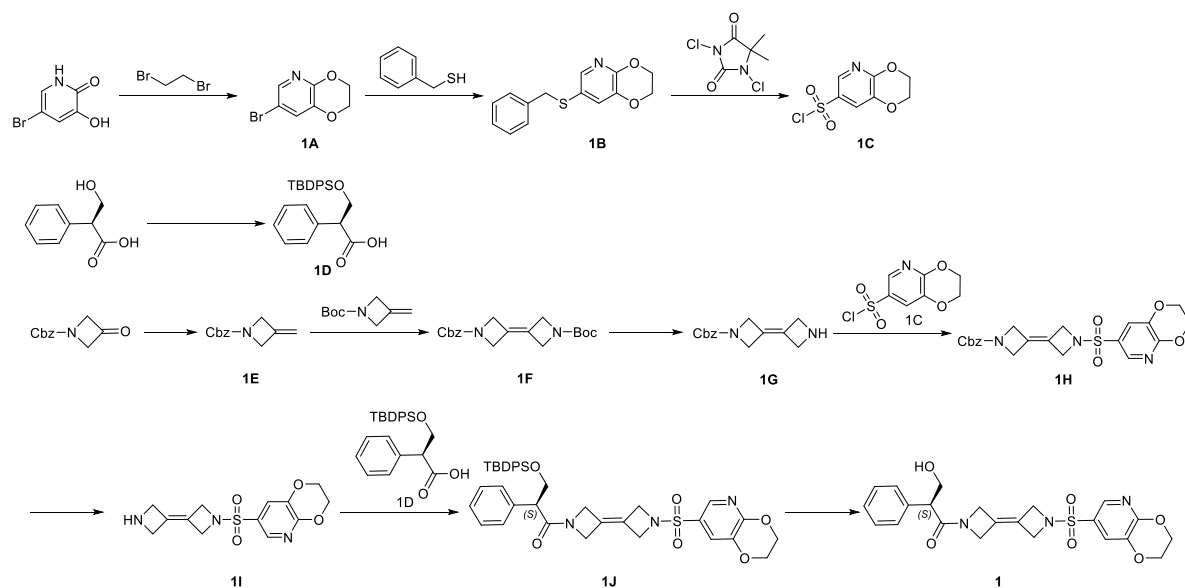
The **compound C** is dissolved in a DMF solution, and then sequentially added with a compound Z-R^B, HATU and DIPEA to conduct a condensation reaction at 25°C. After the reaction was completed, the reaction solution was poured into water and extracted with ethyl acetate for three times, and the organic phases are combined, dried over anhydrous sodium sulfate, filtered, concentrated, and then separated and purified through a chromatography column to obtain **compound D**.

Step 4:

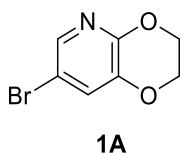
The **compound D** is dissolved in a tetrahydrofuran solution, and then added with tetrabutylammonium fluoride to conduct a deprotection reaction to finally obtain a **compound E**.

Example 1: preparation of (S)-1-(1'-((2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinyldiene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 1**) The synthesis steps were as follows:





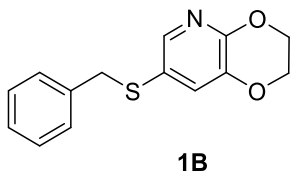
Step 1: preparation of 7-bromo-2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine (compound 1A)



5-bromopyridine-2,3-diol (13.0 g, 68.4 mmol) was dissolved in DMF (130 mL), and then added with 1,2-dibromoethane (19.3 g, 102.6 mmol) and potassium carbonate (28.3 g, 205 mmol), and the reaction system was stirred at 100°C overnight, until the reaction was complete. The reaction solution was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 1A**.

MS (ESI) m/z 216.0 ($M+H$)⁺.

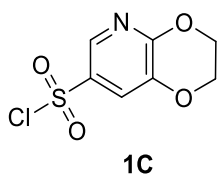
Step 2: preparation of 7-(benzylthio)-2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine (compound 1B)



Under the protection of argon, 7-bromo-2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine (1.0 g, 4.6 mmol) was dissolved in 1,4-dioxane solution (20 mL), and then added with benzyl mercaptan (570 mg, 4.6 mmol), Pd₂(dba)₃ (240 mg, 0.23 mmol), Xantphos (270 mg, 0.46 mmol) and DIPEA (1,190 mg, 9.3 mmol). The reaction system was stirred at 80°C overnight. After the reaction was complete, the reaction solution was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 1B**.

MS (ESI) m/z 260.1 ($M+H$)⁺.

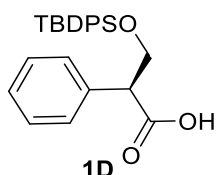
Step 3: preparation of 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride (compound 1C)



7-(benzylthio)-2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine (800 mg, 3 mmol) and 1,3-dichloro-5,5-dimethylhydantoin (820 mg, 6 mmol) were dissolved in a mixed solution of acetonitrile (30 mL), acetic acid (0.75 mL), and water (0.5 mL). The reaction system was stirred at 25°C overnight. After the reaction was complete, the reaction solution was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 1C**.

MS (ESI) m/z 236.0 ($M+H$)⁺.

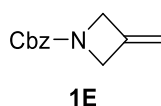
Step 4: preparation of (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid (**compound 1D**)



(*S*)-3-hydroxy-2-phenylpropionic acid (900 mg, 5.4 mmol) and 4-dimethylaminopyridine (1.32 g, 10.8 mmol) were dissolved in dichloromethane (10 mL), and then added with tert-butylchlorodiphenylsilane (1.64 g, 6 mmol). The reaction system was stirred at 25°C overnight. After the reaction was complete, the reaction solution was concentrated to dryness, and the crude product was separated and purified through a C-18 column to obtain **compound 1D**.

MS (ESI) m/z 405.2 ($M+H$)⁺.

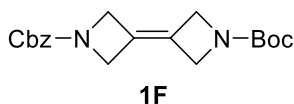
Step 5: Preparation of benzyl 3-methyleneazetidine-1-carboxylate (**compound 1E**)



Benzyl 3-oxoazetidine-1-carboxylate (86.6 g, 268 mmol) and methyltriphenylphosphonium bromide (50 g, 243.5 mmol) were dissolved in tetrahydrofuran (500 mL), and then added with potassium *t*-butoxide (40.9 g, 365.5 mmol). The mixture was stirred at 25°C overnight. After the reaction was complete, the reaction solution was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 1E**.

MS (ESI) m/z 204.1 ($M+H$)⁺.

Step 6: preparation of 1-benzyl 1'-(tert-butyl)-2*H*,2'*H*-[3,3'-diazetidinylidene]-1,1'-(4*H*,4'*H*)-dicarboxylate (**compound 1F**)

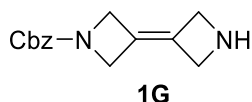


Benzyl 3-methyleneazetidine-1-carboxylate (39 g, 191.9 mmol) and tert-butyl

3-methyleneazetidine-1-carboxylate (32.47 g, 191.9 mmol) were dissolved in dichloroethane (2000 mL), and then added with Grubb's 2 (16.29 g, 19.19 mmol), and the mixture was stirred at 50°C for 48 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 1F**.

5 MS (ESI) m/z 345.2 (M+H)⁺.

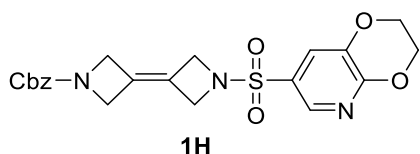
Step 7: preparation of benzyl 1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-carboxylate (**compound 1G**)



10 1-benzyl 1'-(tert-butyl)2*H*,2'*H*-[3,3'-diazetidinylidene]-1,1'(4*H*,4'*H*)-dicarboxylate (3.2 g, 9.29 mmol) was dissolved in ethyl acetate (32 mL), and then added with *p*-toluenesulfonic acid (1.6 g, 9.29 mmol), and the reaction system was stirred at 50°C for 6 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 1G**.

MS (ESI) m/z 245.1 (M+H)⁺.

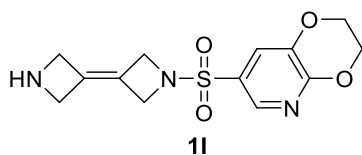
15 **Step 8:** preparation of benzyl 1'-((2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-carboxylate (**compound 1H**)



20 Benzyl 1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-carboxylate (100 mg, 0.41 mmol) and triethylamine (82.5 mg, 0.82 mmol) were dissolved in tetrahydrofuran (4 mL), and then added with 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride (96.5 mg, 0.41 mmol), and the mixture was stirred at 25°C for 2 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 1H**.

MS (ESI) m/z 444.1 (M+H)⁺.

25 **Step 9:** preparation of 7-((1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-ylsulfonyl)-2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine) (**compound 1I**)

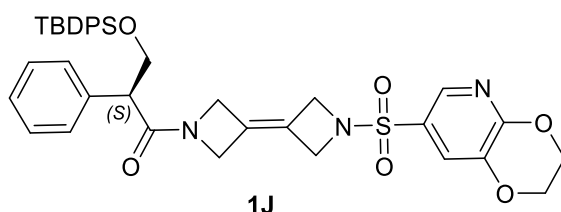


30 Benzyl 1'-((2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-carboxylate (120 mg, 0.27 mmol) was dissolved in trifluoroacetic acid (5 mL), and the reaction system was stirred at 60°C overnight. After the reaction was complete, the reaction

tion solution was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 1I**.

MS (ESI) m/z 310.1 (M+H)⁺.

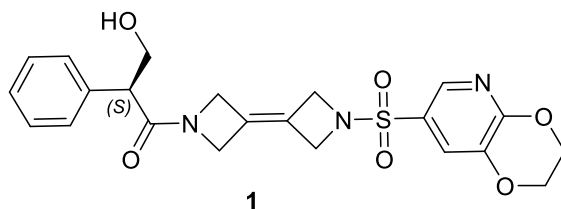
Step 10: preparation of
(S)-3-((tert-butyldiphenylsilyl)oxy)-1-(1'-((2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 1J**)



(S)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid (80 mg, 0.2 mmol) and 7-((1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)sulfonyl)-2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine (61 mg, 0.2 mmol) were dissolved in DMF (5 mL), and then added with HATU (112 mg, 0.3 mmol) and DIPEA (77 mg, 0.6 mmol), and the reaction system was stirred at 25°C for 3 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and subjected to reversed-phase high-pressure liquid chromatography to prepare **compound 1J**.

MS (ESI) m/z 695.3 (M+H)⁺.

Step 11: preparation of
(S)-1-(1'-((2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 1**)

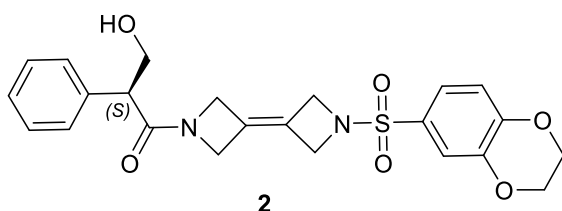


(S)-3-((tert-butyldiphenylsilyl)oxy)-1-(1'-((2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (50 mg, 0.087 mmol) was dissolved in tetrahydrofuran (5 mL), and then added with tetrabutylammonium fluoride (45.5 mg, 0.17 mmol), and the reaction system was stirred at 25°C for 3 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and subjected to reversed-phase high-pressure liquid chromatography to prepare **compound 1** of Example 1.

MS (ESI) m/z 458.2 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.23 (s, 1H), 7.71 (s, 1H), 7.51-7.20 (m, 5H), 4.87 (s, 1H), 4.80-4.72 (m, 1H), 4.60 (s, 2H), 4.50-4.30 (m, 8H), 4.30-4.20 (m, 1H), 3.96 (s, 1H), 3.75-3.55 (m, 2H).

Example 2: preparation of (S)-1-(1'-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 2**):



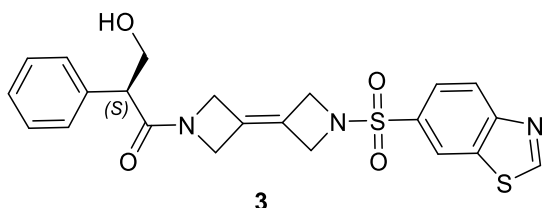
2

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 2,3-dihydrobenzo[*b*][1,4]dioxin-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 2** of Example 2.

5 MS (ESI) m/z 457.1 ($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.35 - 7.20 (m, 7H), 7.13 - 7.11 (m, 1H), 4.85 - 4.7 (m, 2H), 4.40 - 4.20 (m, 11H), 3.95 - 3.85 (m, 1H), 3.75 - 3.70 (m, 1H), 3.50 - 3.40 (m, 1H).

Example 3: preparation of
(*S*)-1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 3**):



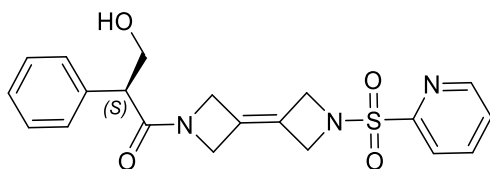
3

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 3** of Example 3.

15 MS (ESI) m/z 456.1 ($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 1H), 8.77 (s, 1H), 8.35-8.24 (m, 1H), 7.90 (d, *J* = 9.4 Hz, 1H), 7.21 (d, *J* = 14.2 Hz, 5H), 4.64 (d, *J* = 12.5 Hz, 2H), 4.34-4.10 (m, 7H), 3.81 (d, *J* = 10.0 Hz, 1H), 3.61-3.50 (m, 1H), 3.40 (d, *J* = 7.1 Hz, 1H).

Example 4: preparation of
(*S*)-3-hydroxy-2-phenyl-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 4**):



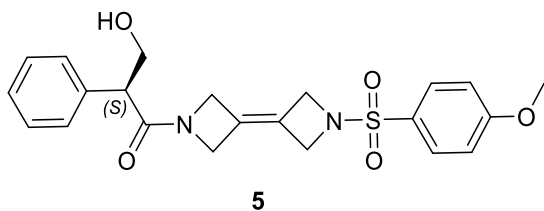
4

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 4** of Example 4.

MS (ESI) m/z 400.0(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.76 (s, 1H), 8.11 (d, J = 11.6 Hz, 1H), 7.95 (d, J = 5.3 Hz, 1H), 7.71 (s, 1H), 7.28-7.19 (m, 5H), 4.68 (d, J = 13.2 Hz, 1H), 4.50 (s, 4H), 4.37-4.23 (m, 2H), 4.17 (d, J = 14.6 Hz, 1H), 3.85 (q, J = 9.0 Hz, 1H), 3.58 (d, J = 10.4 Hz, 1H), 3.50-3.40 (m, 2H).

- 5 **Example** **5:** preparation of
(*S*)-3-hydroxy-1-(1'-((4-methoxyphenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 5**):

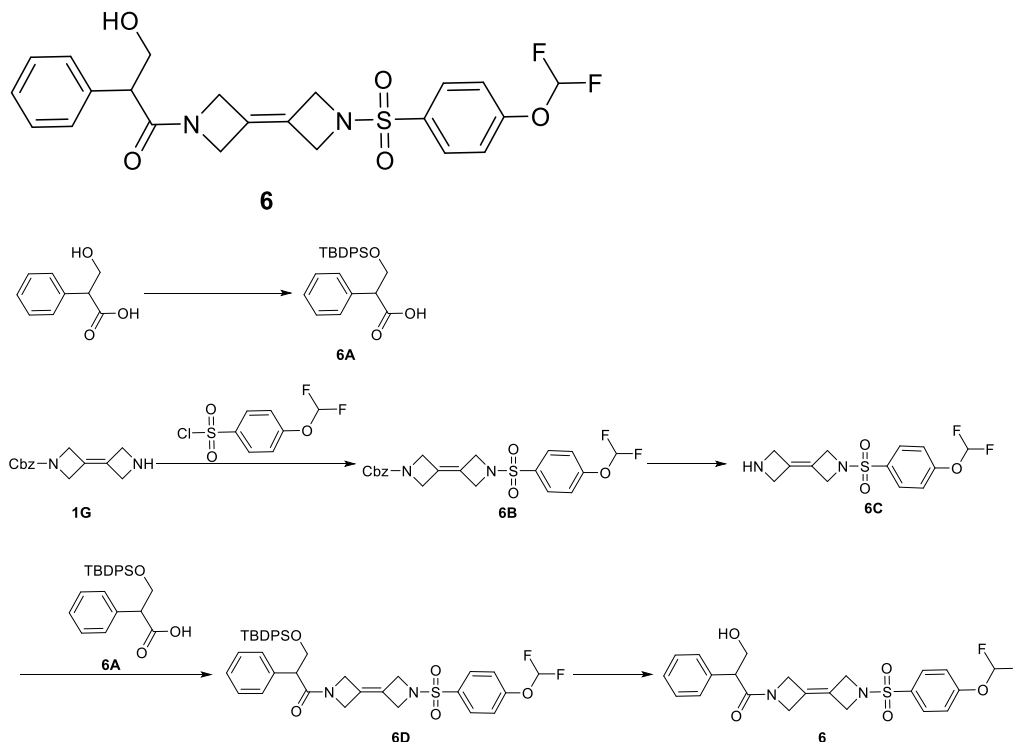


- 10 In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by *p*-methoxybenzenesulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 5** of Example 5.

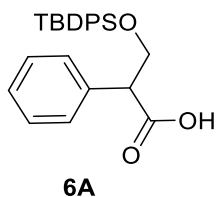
MS (ESI) m/z 429.5(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.80-7.65 (m, 2H), 7.20 (m, 7H), 4.83-4.60 (m, 2H), 4.24 (d, J = 30.9 Hz, 7H), 3.82 (s, 4H), 3.60-3.54 (m, 1H), 3.41 (d, J = 10.1 Hz, 1H).

- 15 **Example** **6:** preparation of
1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 6**):



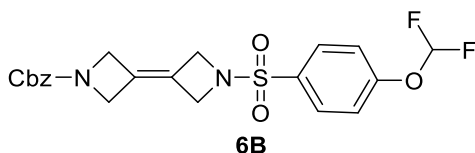
Step 1: preparation of 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid (**compound 6A**)



3-hydroxy-2-phenylpropionic acid (1.0 g, 6.0 mmol) and 4-dimethylaminopyridine (1.47 g, 12 mmol) were dissolved in dichloromethane (10 mL), and then added with tert-butylchlorodiphenylsilane (1.54 g, 9 mmol), and the reaction system was stirred at 25°C overnight. After the reaction was complete, the reaction solution was concentrated to dryness, and separated and purified through a silica gel column to obtain **compound 6A**.

MS (ESI) m/z 405.2 ($M+H$)⁺.

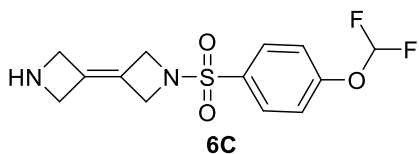
Step 2: preparation of benzyl 1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-carboxylate (**compound 6B**)



Benzyl 3-(azetidin-3-ylidene)azetidine-1-carboxylate (500 mg, 2.05 mmol) and triethylamine (413 mg, 4.1 mmol) were dissolved in tetrahydrofuran solution (20 mL), and then added with 4-(difluoromethoxy)benzenesulfonyl chloride (500 mg, 2.05 mmol), and the reaction system was stirred at 25°C for 3 hours. After the reaction was complete, the reaction solution was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 6B**.

MS (ESI) m/z 451.1 ($M+H$)⁺.

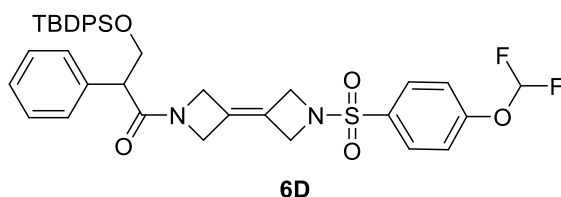
Step 3: preparation of 1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',1',4',4'-tetrahydro-2*H*,2'*H*-3,3'-diazetidinylidene (**compound 6C**)



Benzyl 1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-carboxylate (750 mg, 1.66 mmol) was dissolved in trifluoroacetic acid (5 mL), and the mixture was stirred at 40°C for 16 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 6C**.

MS (ESI) m/z 317.1 ($M+H$)⁺.

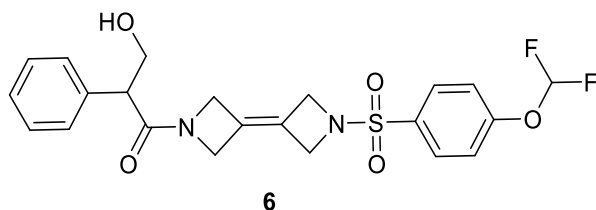
Step 4: preparation of 3-((tert-butyldiphenylsilyl)oxy)-1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 6D**)



5 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid (109 mg, 0.3 mmol) and 1-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-tetrahydro-2*H*,2'*H*-3,3'-diazetidinylidene (85 mg, 0.3 mmol) were dissolved in DMF (5 mL), and then added with HATU (157 mg, 0.4 mmol) and DIPEA (104 mg, 0.8 mmol), and the reaction system was stirred at 25°C for 3 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and subjected to reversed-phase high-pressure liquid chromatography to prepare compound **6D**.

MS (ESI) m/z 703.2 (M+H)⁺.

Step 5: preparation of 1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 6**)

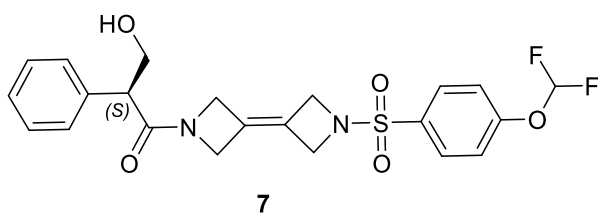


15 3-((tert-butyldiphenylsilyl)oxy)-1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (100 mg, 0.14 mmol) and tetrabutylammonium fluoride (37 mg, 0.14 mmol) were dissolved in tetrahydrofuran (5 mL), and the reaction system was stirred at 25°C for 3 hours. After the reaction was complete, the reaction solution was concentrated to dryness, and subjected to reversed-phase high-pressure liquid chromatography to prepare compound **6** of Example 6.

MS (ESI) m/z 465.2(M+H)⁺.

25 ¹H NMR (400MHz, DMSO-*d*₆) δ 7.91 - 7.88 (m, 2H), 7.45 - 7.43 (m, 2H), 7.30 - 7.20 (m, 5H), 4.72 - 4.69 (m, 1H), 4.60 (s, 2H), 4.36 - 4.15 (m, 7H), 4.95 - 4.85 (m, 1H), 3.65 - 3.60 (m, 1H), 3.50 - 3.40 (m, 1H).

Example 7: preparation of (S)-1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 7**):



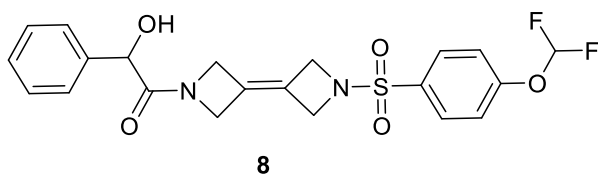
In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by (S)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 7** of Example 7.

5 MS (ESI) m/z 465.1(M+H)⁺.

¹H NMR (400MHz, DMSO-*d*₆) δ 7.91 - 7.88 (m, 2H), 7.45 - 7.43 (m, 2H), 7.30 - 7.20 (m, 5H), 6.06 (s, 1H), 4.72 - 4.69 (m, 1H), 4.36 - 4.15 (m, 7H), 4.95 - 4.85 (m, 1H), 3.65 - 3.60 (m, 1H), 3.50 - 3.40 (m, 2H).

Example 8: preparation of

10 1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)-2-hydroxy-2-phenylethan-1-one (**compound 8**):



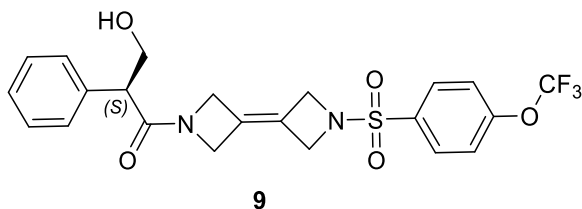
15 In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-hydroxy-2-phenylacetic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 8** of Example 8.

MS (ESI) m/z 451.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 7.90 (m, 2H), 7.45 (s, 2H), 7.30 (d, J = 21.5 Hz, 5H), 5.85 (s, 1H), 5.04 (s, 1H), 4.65 (d, J = 13.9 Hz, 1H), 4.52 (d, J = 14.1 Hz, 1H), 4.29 (s, 6H).

Example 9: preparation of

20 (S)-3-hydroxy-2-phenyl-1-((4-(trifluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)propan-1-one (**compound 9**):

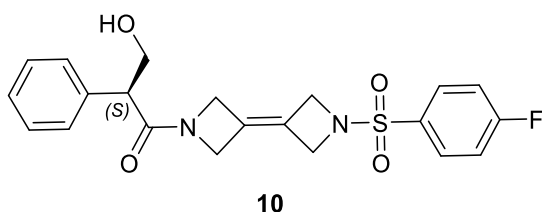


25 In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 4-(trifluoromethoxy)benzenesulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 9** of Example 9.

MS (ESI) m/z 483.1(M+H)⁺.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.99-7.96(m, 2H), 7.67-7.65 (d, $J = 0.8$ Hz, 2H), 7.30-7.22 (m, 5H), 4.81-4.69 (m, 2H), 4.36-4.18 (m, 7H), 3.90-3.86 (t, $J = 0.8$ Hz, 1H), 3.63-3.60 (m, 1H), 3.47-3.43 (m, 1H).

Example 10: preparation of
 5 (S)-1-(1'-(4-fluorophenyl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 10**):

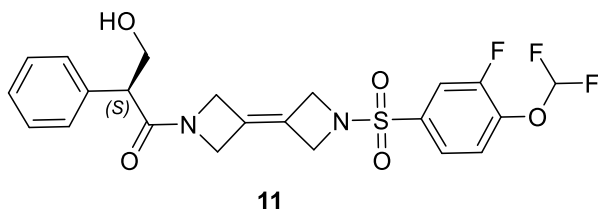


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 4-fluorobenzenesulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 10** of Example 10.

MS (ESI) m/z 417.1(M+H) $^+$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.99-7.96(m, 2H), 7.67-7.65 (d, $J = 0.8$ Hz, 2H), 7.30-7.22 (m, 5H), 4.81-4.69 (m, 2H), 4.36-4.18 (m, 7H), 3.90-3.86 (t, $J = 0.8$ Hz, 1H), 3.63-3.60 (m, 1H), 3.47-3.43 (m, 1H).

Example 11: preparation of
 15 (S)-1-(1'-(3-fluoro-4-difluoromethoxyphenyl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 11**):

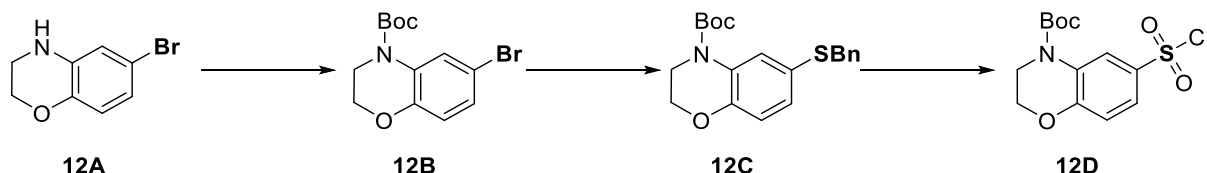
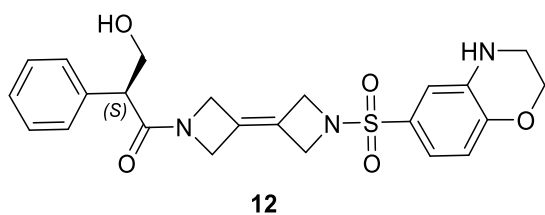


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 3-fluoro-4-difluoromethoxybenzenesulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 11** of Example 11.

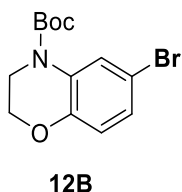
MS (ESI) m/z 483.1(M+H) $^+$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.92-7.89 (m, 1H), 7.89-7.62 (m, 2H), 7.44-7.22 (m, 6H), 4.82-4.79 (m, 1H), 4.72-4.69 (d, $J = 28.0$ Hz, 1H), 4.34-4.20 (m, 7H), 3.89-3.84 (m, 1H), 3.64-3.58 (m, 1H), 3.47-3.43 (m, 1H).

Example 12: preparation of
 (S)-1-(1'-((3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 12**):



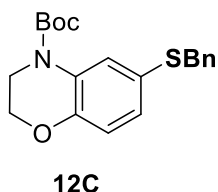
Step 1: Preparation of tert-butyl 6-bromo-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (**compound 12B**)



6-bromo-3,4-dihydro-2H-1,4-benzoxazine (2 g, 9.34 mmol), 4-dimethylaminopyridine (114 mg, 0.93 mmol) and triethylamine (1.42 g, 14 mmol) were dissolved in tetrahydrofuran (40 mL), then added with di-tert-butyl dicarbonate (2 g, 9.34 mmol), and the reaction system was stirred at 40°C for 16 hours. After the reaction was complete, the reaction solution was poured into water, and extracted with ethyl acetate (60 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 12B**.

MS (ESI) m/z 314.0 (M+H)⁺.

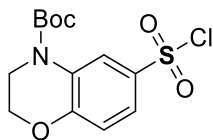
Step 2: preparation of tert-butyl 6-(benzylthio)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (**compound 12C**)



Tert-butyl 6-bromo-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (500 mg, 1.59 mmol), benzyl mercaptan (236.8 mg, 1.91 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (92 mg, 0.16 mmol), tris(dibenzylideneacetone)dipalladium (73 mg, 0.07 mmol) and *N,N*-diisopropylethylamine (617 mg, 4.77 mmol) were dissolved in 1,4-dioxane (10 mL), and the reaction system was placed and stirred at 40°C for 16 hours. After the reaction was complete, the reaction solution was poured into water, the aqueous phase was extracted with ethyl acetate (40 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. After the organic phase was concentrated to dryness under reduced pressure, the residue was separated and purified through a silica gel column to obtain **compound 12C**.

MS (ESI) m/z 358.1 (M+H)⁺.

Step 3: preparation of tert-butyl 6-(chlorosulfonyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (**compound 12D**)



12D

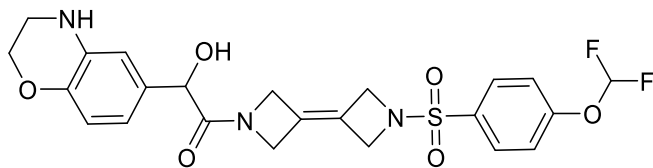
- 5 Tert-butyl 6-(benzylthio)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (500 mg, 1.39 mmol) was dissolved in a mixed solvent (acetonitrile: acetic acid: water = 40:1.5:1, 25 mL), and added with 1,3-dichloro-5,5-dimethylhydantoin (547.6 mg, 2.78 mmol) with stirring at 0°C. Then stirring was conducted at room temperature for 3 hours. After the reaction was complete, the reaction solution was poured into water, and extracted with ethyl acetate (60 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. The organic phase was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 12D**.

- 15 In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by tert-butyl 6-(chlorosulfonyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate, and the same preparation method as that of Example 1 was adopted to obtain **compound 12** of Example 12.

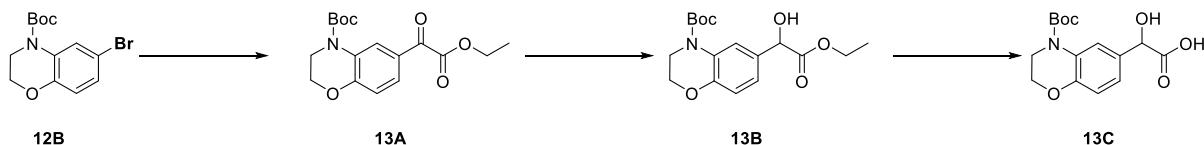
MS (ESI) m/z 456.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.34-7.21 (m, 6H), 7.0 (s, 1H), 6.89-6.84 (m, 2H), 6.33 (s, 1H), 4.82-4.79 (t, *J* = 0.8 Hz, 1H), 4.73-4.70 (d, *J* = 1.2 Hz, 1H), 4.38-4.21 (m, 10H), 3.91-3.85 (m, 1H), 3.63-3.59 (m, 1H), 3.47-3.43 (m, 1H).

- 20 **Example 13:** preparation of 1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-2-hydroxyethan-1-one (**compound 13**):



13



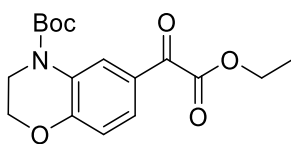
12B

13A

13B

13C

- 25 **Step 1:** preparation of tert-butyl 6-(2-ethoxy-2-oxoacetyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (**compound 13A**)

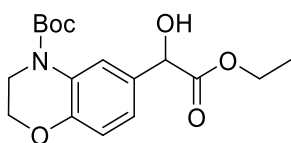


13A

Tert-butyl 6-bromo-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (500 mg, 1.59 mmol) was added into dry tetrahydrofuran (10 mL). The reaction system was replaced with nitrogen for three times and then maintained as a nitrogen system, cooled to -78°C, slowly added dropwise with *n*-butyllithium (122 mg, 1.91 mmol), and then stirred at -78°C for 0.5 hours. Diethyl oxalate (256 mg, 1.75 mmol) was added dropwise into the reaction solution, then heated to room temperature after the dropwise addition, and stirred for 1 hour. After the reaction was complete, the reaction solution was poured into water, the aqueous phase was extracted with ethyl acetate (40 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. The organic phase was concentrated to dryness and then separated and purified through a silica gel column to obtain **compound 13A**.

MS (ESI) *m/z* 336.1 (M+H)⁺.

Step 2: preparation of tert-butyl 6-(2-ethoxy-1-hydroxy-2-oxoethyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (**compound 13B**)

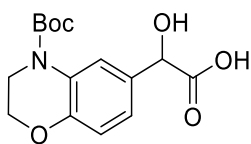


13B

Tert-butyl 6-(2-ethoxy-2-oxoacetyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (170 mg, 0.50 mmol) was added into tetrahydrofuran (8 mL), and added with sodium borohydride (29 mg, 0.76 mmol) with stirring at 0°C. Then stirring was conducted at room temperature for 0.5 hours. After the reaction was complete, the reaction solution was poured into water, and extracted with ethyl acetate (30 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. After the organic phase was concentrated to dryness under reduced pressure, the residue was separated and purified through a silica gel column to obtain **compound 13B**.

MS (ESI) *m/z* 338.1 (M+H)⁺.

Step 3: preparation of 2-(4-(tert-butoxycarbonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-2-hydroxyacetic acid (**compound 13C**)



13C

Tert-butyl 6-(2-ethoxy-1-hydroxy-2-oxoethyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (170 mg, crude product) and lithium hydroxide hydrate (106 mg, 2.52 mmol) were added into a mixed solution of tetrahydrofuran (3 mL) and water (3 mL), and stirred at room temperature for 16 hours.

- 5 After the reaction was complete, the reaction solution was adjusted to pH 4-5 with 2N hydrochloric acid solution in ice bath, diluted with water, and then extracted with ethyl acetate (20 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated to dryness, and the residue was separated and purified through a silica gel column to obtain **compound 13C**.

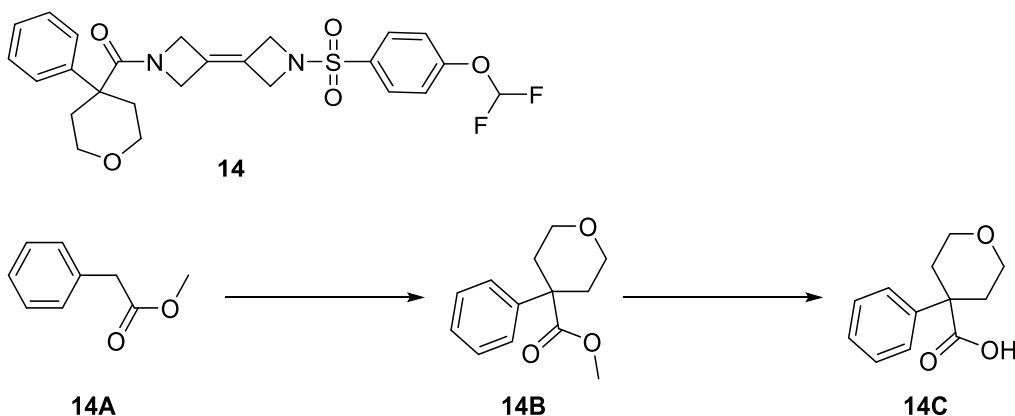
- 10 MS (ESI) *m/z* 310.1 (M+H)⁺.

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-(tert-butoxycarbonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-2-hydroxyacetic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 13** of Example 13.

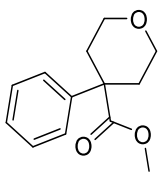
MS (ESI) *m/z* 508.1(M+H)⁺.

- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95-7.88 (d, *J* = 8 Hz, 2H), 7.49-7.43 (d, *J* = 8 Hz, 3H), 6.56-6.51 (m, 2H), 6.41-6.39 (m, 1H), 5.76 (s, 1H), 5.49-5.48 (d, *J* = 4 Hz, 1H), 4.81-4.79 (d, *J* = 8 Hz, 1H), 4.61-4.57 (d, *J* = 16 Hz, 1H), 4.42-4.38 (d, *J* = 16 Hz, 1H), 4.27 (s, 6H), 4.07-4.05 (m, 2H), 3.22 (s, 2H).

Example 14: preparation of (1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinyldiene]-1(4*H*)-yl)(4-phenyltetrahydro-2*H*-pyran-4-yl)methanone (**compound 14**):



Step 1: preparation of methyl 4-phenyltetrahydro-2*H*-pyran-4-carboxylate (**compound 14B**)

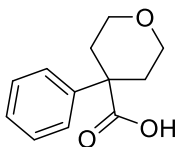


14B

Methyl 2-phenyl acetate (2.0 g, 13.32 mmol) was dissolved in tetrahydrofuran (40.0 mL), the temperature of the reaction system was reduced to 0°C, and then the reaction system was slowly added with sodium hydride (1.06 g, 26.64 mmol) in portions. The reaction solution was stirred at 0°C for 30 minutes, and then added dropwise with 2-iodoethyl ether (3.47 g, 10.65 mmol). After the dropwise addition was completed, the reaction system was stirred at 0°C for 10 minutes and then slowly heated to room temperature. The reaction system was then heated to 50°C and stirred for 18 hours. After the reaction was complete, water was added to quench the reaction. The aqueous phase was extracted with ethyl acetate (50 mL*3). The organic phases were combined, washed with a saturated brine, dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 14B**.

MS (ESI) m/z 221.1 (M+H)⁺.

Step 2: preparation of 4-phenyltetrahydro-2H-pyran-4-carboxylic acid (**compound 14C**)



14C

Methyl 4-phenyltetrahydro-2H-pyran-4-carboxylate (1.0 g, 4.54 mmol) was dissolved in methanol (10.0 mL) and water (10.0 mL), and then added with sodium hydroxide (544.8 mg, 13.62 mmol), and the reaction solution was stirred at 50°C for 3 hours. After the reaction was complete, the reaction system was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (50 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. After the organic phase was concentrated to dryness under reduced pressure, the residue was separated and purified through a silica gel column to obtain **compound 14C**.

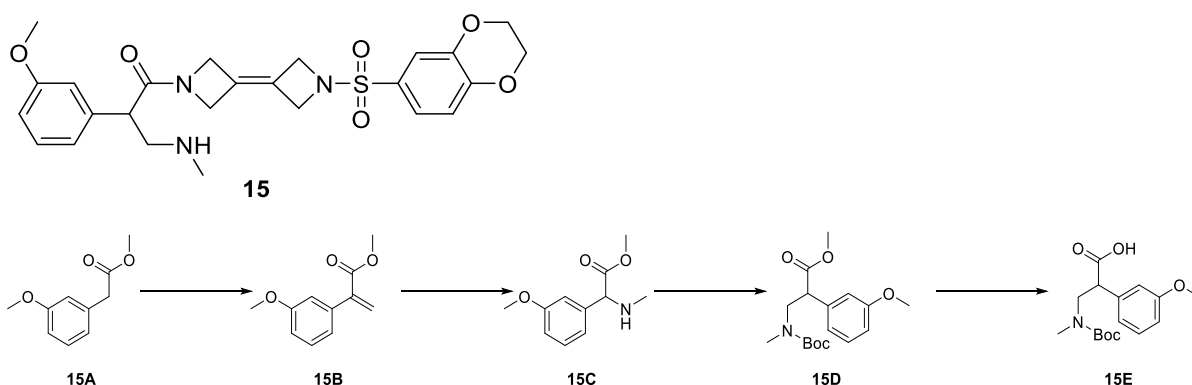
MS (ESI) m/z 338.1 (M+H)⁺.

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 4-phenyltetrahydro-2H-pyran-4-carboxylic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 14** of Example 14.

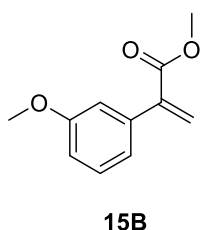
MS (ESI) m/z 505.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88-7.84 (m, 2H), 7.46-7.23 (m, 8H), 4.30-4.10 (m, 6H), 3.97 (s, 2H), 3.78-3.63 (m, 2H), 3.52 (t, J = 11.0 Hz, 2H), 2.15 (d, J = 13.5 Hz, 2H), 1.91-1.72 (m, 2H).

Example 15: preparation of 1-(1'-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(3-methoxyphenyl)-3-(methylamino)propan-1-one (**compound 15**):

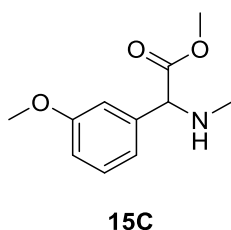


Step 1: preparation of methyl 2-(3-methoxyphenyl)acrylate (compound 15B)



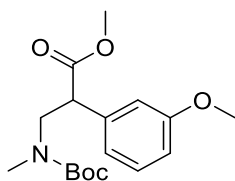
- 5 Methyl 2-(3-methoxyphenyl)acetate (2.00 g, 11.10mmol) was added into *N,N*-dimethyl formamide (20.0 mL), and then sequentially added with potassium carbonate (3.83 g, 27.75 mmol), trioxymethylene (1.19 g, 13.32mmol) and tetrabutylammonium iodide (410.0 mg, 1.11 mmol). The reaction solution was reacted at 80°C for half an hour. After the reaction was complete, it was separated and conducted through a silica gel column to obtain **compound 15B**.
- 10 MS (ESI) m/z 193.1 ($M+H$)⁺.

Step 2: Preparation of methyl 2-(3-methoxyphenyl)-2-(methylamino)acetate (compound 15C)



- 15 Methyl 2-(3-methoxyphenyl)acrylate (2.02 g, 10.5 mmol) was added into methylamine tetrahydrofuran solution (20.0 mL), and the reaction was carried out at room temperature for 4 hours, separated and purified through a silica gel column to obtain **compound 15C**.
- MS (ESI) m/z 224.1 ($M+H$)⁺.

Step 3: preparation of methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxyphenyl)propionate (compound 15D)

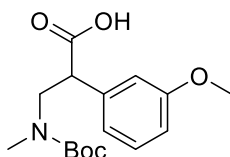


15D

Methyl 2-(3-methoxyphenyl)-2-(methylamino)acetate (2.00 g, 8.96 mmol) and 4-dimethylaminopyridine were dissolved in dichloromethane (10.0 mL), and added with triethylamine (1.81 g, 17.92 mmol) and di-tert-butyl dicarbonate (1.95 g, 8.96 mmol). Reaction was conducted at room temperature for two hours. After the reaction was complete, the reaction system was added with water to quench the reaction, and adjusted to pH 5-6 with 2N hydrochloric acid aqueous solution. Then the reaction system was extracted with ethyl acetate (20.0 mL*3). The organic layers were combined, washed with saturated sodium chloride (20.0 mL), and dried over anhydrous sodium sulfate. After the organic phase was concentrated to dryness under reduced pressure, the residue was separated and purified through a silica gel column to obtain **compound 15D**.

MS (ESI) m/z 324.2 (M+H)⁺.

Step 4: preparation of 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxyphenyl)propionic acid (**compound 15E**)



15E

Methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxyphenyl)propionate (669.0 mg, 2.07 mmol) was dissolved in tetrahydrofuran (5.0 mL) and water (5.0 mL), and added with lithium hydroxide (99.1 mg, 4.14 mmol). The reaction was carried out at room temperature for 16 hours. After the reaction was complete, the organic phase was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 15E**.

MS (ESI) m/z 310.2 (M+H)⁺.

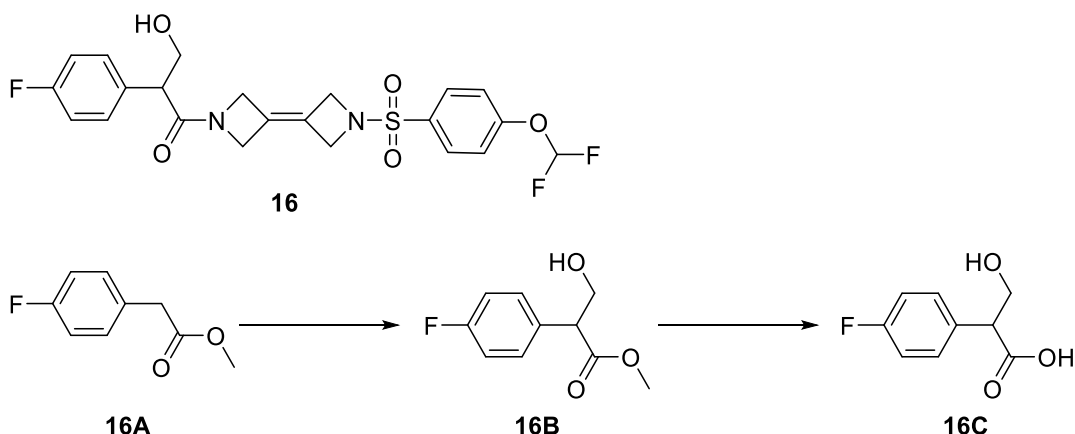
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 2,3-dihydrobenzo[*b*][1,4]dioxin-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxyphenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 15** of Example 15.

MS (ESI) m/z 500.2 (M+H)⁺.

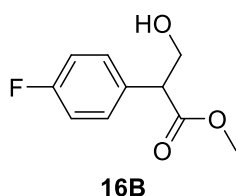
¹H NMR (400MHz, DMSO-*d*₆) δ 7.28-7.22 (m, 3H), 7.06-7.04 (m, 1H), 6.85-6.81 (m, 3H), 4.34-4.30 (m, 6H), 4.10-3.81 (m, 9H), 3.71 (s, 3H), 3.15-3.04 (m, 1H), 2.28 (s, 3H).

Example 16: preparation of 1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(

4-fluorophenyl)-3-hydroxypropan-1-one (**compound 16**):



Step 1: preparation of methyl 2-(4-fluorophenyl)-3-hydroxypropionate (**compound 16B**)

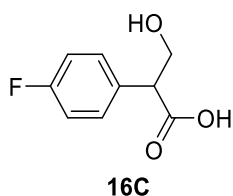


5

Methyl 4-fluorophenylacetate (1.0 g, 5.95 mmol) and paraformaldehyde (562.5 mg, 6.24 mmol) were dissolved in dimethyl sulfoxide (40.0 mL), and then added with sodium methoxide (16.1 mg, 0.30 mmol). The reaction solution was reacted at room temperature for 4 hours. When the reaction was complete, the reaction system was added with water to quench the reaction. The aqueous phase was extracted with ethyl acetate (50 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. After the organic phase was concentrated to dryness under reduced pressure, the residue was separated and purified through a silica gel column to obtain **compound 16B**.

MS (ESI) m/z 199.1 ($M+H$)⁺.

15 **Step 2:** preparation of 2-(4-fluorophenyl)-3-hydroxypropionic acid (**compound 16C**)



20 Methyl 2-(4-fluorophenyl)-3-hydroxypropionate (600.0 mg, 3.03 mmol) was dissolved in methanol (9.0 mL) and water (6.0 mL), and then added with sodium hydroxide (242.2 mg, 6.05 mmol), and the reaction solution was stirred at 50°C for 3 hours. After the reaction was complete, the reaction solution was adjusted to pH = 2 with 1N hydrochloric acid aqueous solution, and extracted with dichloromethane (50 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. It was concentrated to obtain a white solid compound, and the residue was separated and purified through a silica gel column to obtain **compound 16C**.

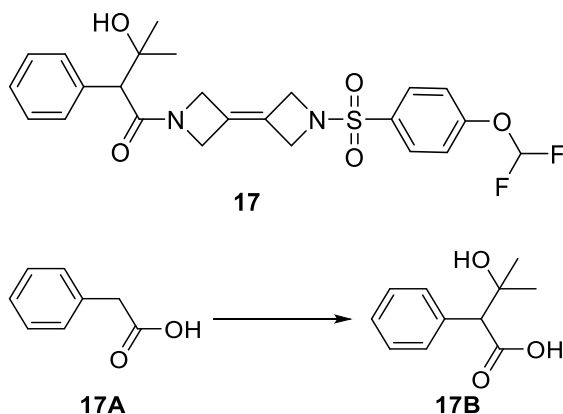
MS (ESI) m/z 185.1 (M+H)⁺.

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 16** of Example 16.

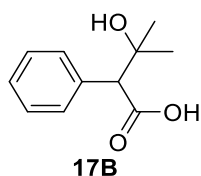
5 MS (ESI) m/z 483.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91-7.89 (d, *J* = 7.7 Hz, 2H), 7.63-7.29 (m, 5H), 7.12-7.09 (m, 2H), 4.85 (s, 1H), 4.70 (d, *J* = 12.7 Hz, 1H), 4.39-4.22 (m, 7H), 3.85-3.83 (m, 1H), 3.70-3.64 (m, 1H), 3.51-3.41 (m, 1H).

Example 17: preparation of 1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-3-methyl-2-phenylbutan-1-one (**compound 17**):



Step 1: preparation of 3-hydroxy-3-methyl-2-phenylbutyric acid (**compound 17B**)



15

2-phenylacetic acid (0.7 g, 5.14 mmol) was dissolved in tetrahydrofuran (11.0 mL), and added dropwise with isopropylmagnesium chloride (1.06 g, 10.28 mmol, 2M) at room temperature, and the reaction solution was stirred at 40°C for 1 hour after the dropwise addition. Then acetone (328.5 mg, 5.66 mmol) was added, and the reaction solution was continued to be stirred at 40°C for 1 hour. The reaction solution was adjusted to pH = 2 with 3N hydrochloric acid, the aqueous phase was extracted with dichloromethane (50 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. It was concentrated to obtain a white solid compound, and the residue was separated and purified through a silica gel column to obtain **compound 17B**.

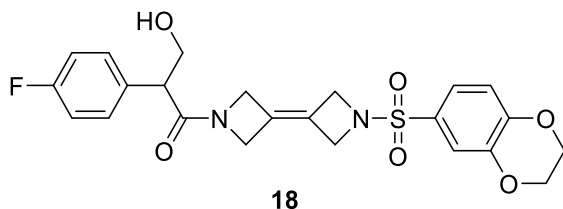
MS (ESI) m/z 195.1 (M+H)⁺.

25 In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-3-methyl-2-phenylbutyric acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 17** of Example 17.

MS (ESI) m/z 493.2 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90-7.88 (m, 2H), 7.63-7.19 (m, 8H), 4.91 (s, 1H), 4.75-4.72 (d, *J* = 13.3 Hz, 1H), 4.28-4.22 (m, 7H), 3.50 (s, 1H), 1.13 (s, 3H), 0.98 (s, 3H).

Example 18: preparation of 1-(1'-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 18**):

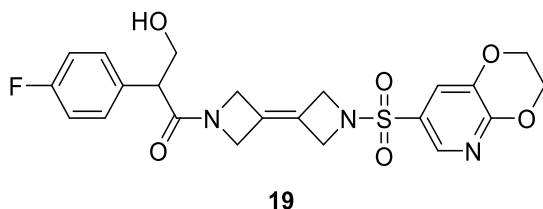


In step 10 of Example 1, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxyphenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 18** of Example 18.

MS (ESI) m/z 475.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.34-7.24 (m, 4H), 7.14-7.10 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 4.83-4.81 (m, 1H), 4.31-4.30 (m, 5H), 4.00-3.85 (m, 8H), 3.52-3.39 (m, 2H).

Example 19: preparation of 1-(1'-((2,3-dihydro-[1,4]dioxolane[2,3-*b*]pyridin-7-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 19**):

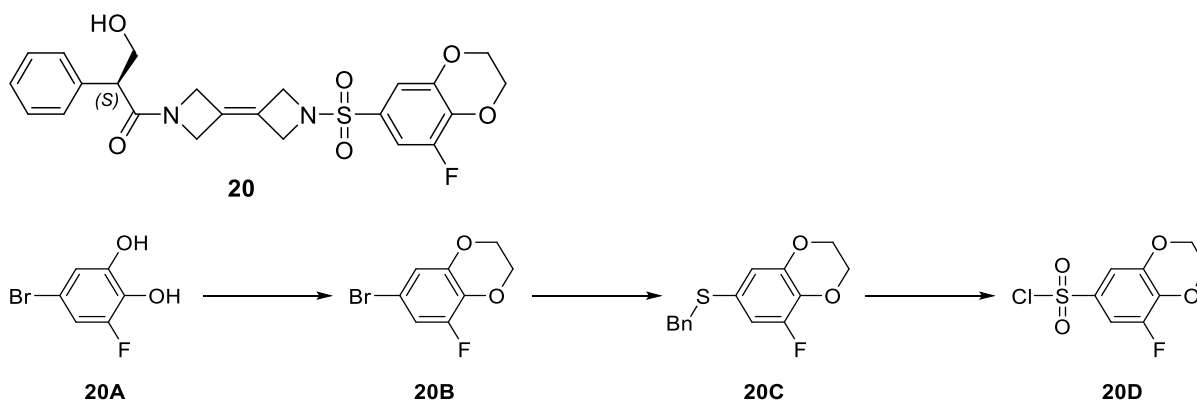


In step 10 of Example 1, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 19** of Example 19.

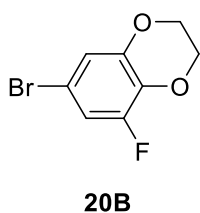
MS (ESI) m/z 476.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.28(s, 1H), 7.66 (s, 1H), 7.33-7.27 (m, 2H), 7.17 - 7.10 (m, 2H), 4.87 - 4.85 (m, 1H), 4.75 - 4.68 (m, 1H), 4.55-4.53 (m, 2H), 4.40 - 4.21 (m, 9H), 3.85-3.80 (m, 1H), 3.70 - 3.55 (m, 2H).

Example 20: preparation of (*S*)-1-(1'-((8-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 20**):



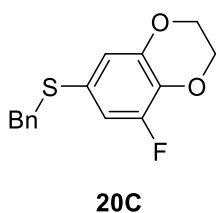
Step 1: preparation of 7-bromo-5-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxin (**compound 20B**)



5 5-bromo-3-fluorobenzene-1,2-diol (500 mg, 2.42 mmol), 1,2-dibromoethane (680.67 mg, 3.62 mmol), and potassium carbonate (1.0 g, 7.25 mmol) were added into *N,N*-dimethylformamide (5 mL), and finally the reaction system was stirred at 100°C for 16 hours. After the reaction was complete, the reaction solution was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 20B**.

10 MS (ESI) *m/z* 233.0 (*M*+*H*)⁺.

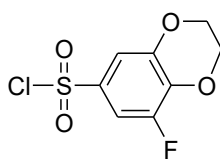
Step 2: preparation of 7-(benzylthio)-5-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxin (**compound 20C**)



15 7-bromo-5-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxin (330 mg, 1.42 mmol), benzyl mercaptan (175.88 mg, 1.42 mmol), *N,N*-diisopropylethylamine (365.35 mg, 2.83 mmol), tris(dibenzylideneacetone)dipalladium-chloroform adduct (64.84 mg, 70.81 μmol), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (81.94 mg, 141.61 μmol) were added into 1,4-dioxane (6 mL), and finally the reaction system was placed and stirred at 80°C for 16 hours. After the reaction was complete, the reaction solution was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 20C**.

20 MS (ESI) *m/z* 277.1 (*M*+*H*)⁺.

Step 3: preparation of 8-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxin-6-sulfonyl chloride (**compound 20D**)



20D

7-(benzylthio)-5-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxin (200 mg, 723.78 μ mol) and 1,3-dichloro-5,5-dimethylhydantoin (285.20 mg, 1.45 mmol) were added into acetonitrile (7.5 mL), acetic acid (0.19 mL) and water (0.13 mL), and then the reaction system was stirred at 25°C for 16 hours. After the reaction was complete, the reaction solution was concentrated to dryness under reduced pressure, and the residue was separated and purified through a silica gel column to obtain **compound 20D**.

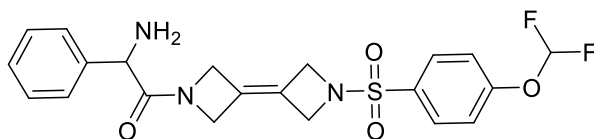
MS (ESI) m/z 253.0 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 8-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxin-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 20** of Example 20.

MS (ESI) m/z 475.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.31-7.15 (m, 7H), 4.73- 4.70 (d, *J* = 13.0 Hz, 1H), 4.42 -4.30 (m, 12H), 3.90-3.87 (m, 1H), 3.47-3.44 (m, 1H), 3.33-3.31 (m, 1H).

Example 21: preparation of 2-amino-1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylethan-1-one (**compound 21**):



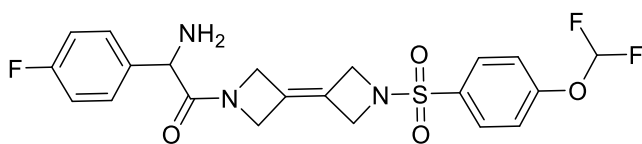
21

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-((tert-butoxycarbonyl)amino)-2-phenylacetic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 21** of Example 21.

MS (ESI) m/z 450.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.91-7.89 (m, 2H), 7.45-7.43 (m, 3H), 7.32-7.22 (m, 5H), 4.72-4.69 (d, *J* = 10.4 Hz, 1H), 4.37-4.19 (m, 8H), 2.12 (s, 2H).

Example 22: preparation of 2-amino-1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)ethan-1-one (**compound 22**):



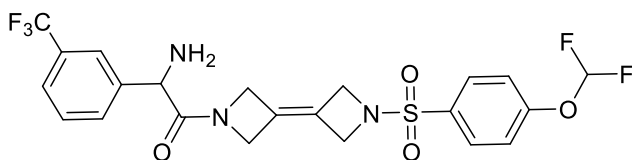
22

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-((tert-butoxycarbonyl)amino)-2-(4-fluorophenyl)acetic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 22** of Example 22.

5 MS (ESI) m/z 468.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.91-7.89 (d, *J* = 8.8 Hz, 2H), 7.46-7.27 (m, 5H), 7.14-7.10 (m, 2H), 4.69 (s, 1H), 4.40-4.22 (m, 8H), 2.34-2.32 (m, 2H).

Example 23: preparation of 2-amino-1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(3-(trifluoromethyl)phenyl)ethan-1-one (**compound 23**):



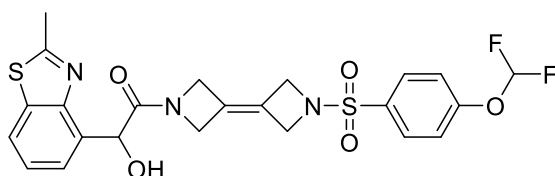
23

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethyl)phenyl)acetic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 23** of Example 23.

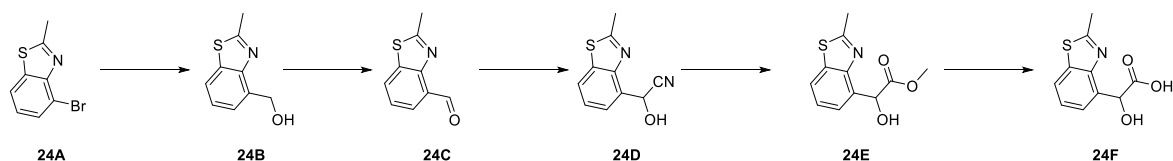
15 MS (ESI) m/z 518.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.92-7.90 (d, *J* = 8.8 Hz, 2H), 7.67-7.51 (m, 4H), 7.46-7.44 (d, *J* = 8.5 Hz, 2H), 4.80-4.75 (d, *J* = 13.7 Hz, 1H), 4.53-4.21 (m, 8H), 2.33-2.27 (d, *J* = 24.7 Hz, 2H).

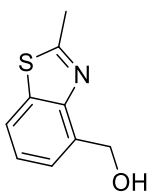
Example 24: preparation of 1-(1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-hydroxy-2-(2-methylbenzo[*d*]thiazol-1-yl)ethan-1-one (**compound 24**):



24



Step 1: preparation of 2-methyl-4-hydroxymethylbenzo[*d*]thiazole (**compound 24B**):

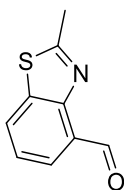


24B

4-bromo-2-methyl-1,3-benzothiazole (200 mg, 876.77 μmol) and tributylstannyl methanol (430 mg, 1.34 mmol) were dissolved in 1,4-dioxane (5 mL), and added with tetrakis(triphenylphosphine)palladium (100 mg, 86.58 μmol) at room temperature, and the resulting mixture was stirred at 100°C for 16 hours under the protection of nitrogen. After being cooled to room temperature, the reaction mixture was quenched with saturated ammonium chloride aqueous solution, the aqueous phase was extracted with ethyl acetate (10 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 24B**.

MS (ESI) m/z 180.0 ($M+H$)⁺.

Step 2: preparation of 2-methylbenzo[d]thiazole-4-carbaldehyde (**compound 24C**):

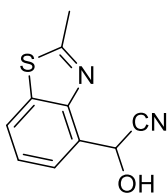


24C

At -78°C, oxalyl chloride (70 mg, 551.50 μmol) was slowly added dropwise into a solution of dimethyl sulfoxide (65 mg, 831.91 μmol) in dichloromethane (3 mL), and the resulting mixture was stirred at -78°C under the protection of nitrogen for 0.5 hours. Then a solution of 2-methyl-4-hydroxymethylbenzo[d]thiazole (50 mg, 278.96 μmol) in dichloromethane (2 mL) was added at the same temperature, the resulting mixture was stirred at this temperature for 1 hour and then added with triethylamine (0.3 mL), and the resulting mixture was continuously stirred for 0.5 hours, heated to room temperature, and then stirred for further 0.5 hours. After the reaction was complete, the reaction mixture was quenched with 10 mL brine. The aqueous phase was extracted with ethyl acetate (10 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 24C**.

MS (ESI) m/z 178.0($M+H$)⁺.

Step 3: preparation of 2-hydroxy-2-(2-methylbenzo[d]thiazol-4-yl)acetonitrile (**compound 24D**):

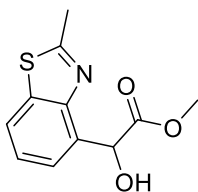


24D

2-methyl-1,3-benzothiazole-4-carbaldehyde (110 mg, 620.69 μmol) was dissolved in dichloromethane (3 mL), and added with trimethylsilyl cyanide (180 mg, 1.82 mmol) and zinc iodide (100 mg, 313.48 μmol) at room temperature. The resulting mixture was stirred at room temperature under the protection of nitrogen for 2 hours. The reaction mixture was quenched with 10 mL of brine. The aqueous phase was extracted with ethyl acetate (10 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 24D**.

MS (ESI) m/z 205.1 ($M+H$)⁺.

Step 4: preparation of methyl 2-hydroxy-2-(2-methylbenzo[d]thiazol-4-yl)acetate (**compound 24E**):

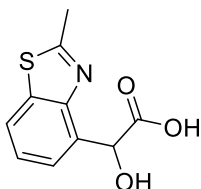


24E

2-hydroxy-2-(2-methyl-1,3-benzothiazol-4-yl)acetonitrile (110 mg, 538.56 μmol) was dissolved in methanol (3 mL), and then added dropwise with concentrated hydrochloric acid (3 mL), and the resulting mixture was stirred at 60°C for 2 hours under the protection of nitrogen. After the reaction was ended, the reaction mixture was concentrated and the pH value of the solution was adjusted to 7-8 with saturated sodium bicarbonate aqueous solution. The aqueous phase was extracted with ethyl acetate (10 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 24E**.

MS (ESI) m/z 238.0 ($M+H$)⁺.

Step 5: preparation of 2-hydroxy-2-(2-methylbenzo[d]thiazol-4-yl)acetic acid (**compound 24F**):



24F

Methyl 2-hydroxy-2-(2-methyl-1,3-benzothiazol-4-yl)acetate (125 mg, 526.82 μmol) was dissolved in a mixed solution of tetrahydrofuran (3 mL) and water (3 mL), and then added with lithium hydroxide

monohydrate (100 mg, 2.44 mmol), and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated, and the pH value of the solution was adjusted to 5-6 with 2N diluted hydrochloric acid. The aqueous phase was extracted with ethyl acetate (10 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 24F**.

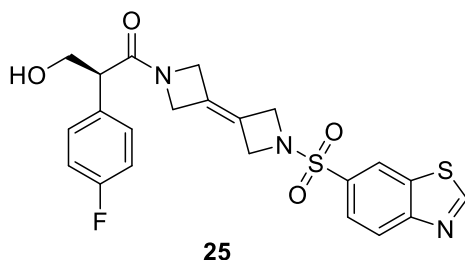
MS (ESI) m/z 224.1 (M+H)⁺.

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-hydroxy-2-(2-methylbenzo[*d*]thiazol-4-yl)acetic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 24** of Example 24.

MS (ESI) m/z 522.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.96 - 7.90 (m, 3H), 7.65 - 7.29 (m, 5H), 5.88 - 5.78 (m, 2H), 4.85 - 4.59 (m, 2H), 4.31 - 4.23 (m, 6H), 2.77 (s, 3H).

Example 25: preparation of (S)-1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 25**):

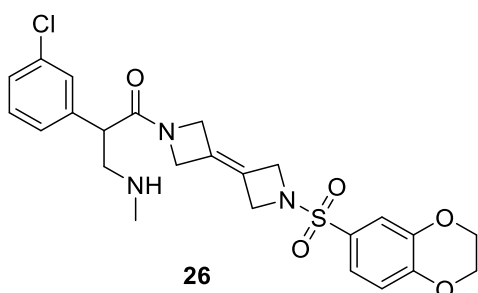


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (S)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 25** of Example 25.

MS (ESI) m/z 474.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.69 (s, 1H), 8.82 (s, 1H), 8.35-8.33 (d, *J* = 8.0 Hz, 1H), 7.96-7.94 (d, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 2H), 7.13-7.08 (m, 2H), 4.82 (s, 1H), 4.69-4.66 (d, *J* = 12.0 Hz, 1H), 4.35-4.16 (m, 8H), 3.83 (s, 1H), 3.64-3.61 (m, 1H).

Example 26: preparation of 2-(3-chlorophenyl)-1-(1'-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-(methylamino)propan-1-one (**compound 26**):

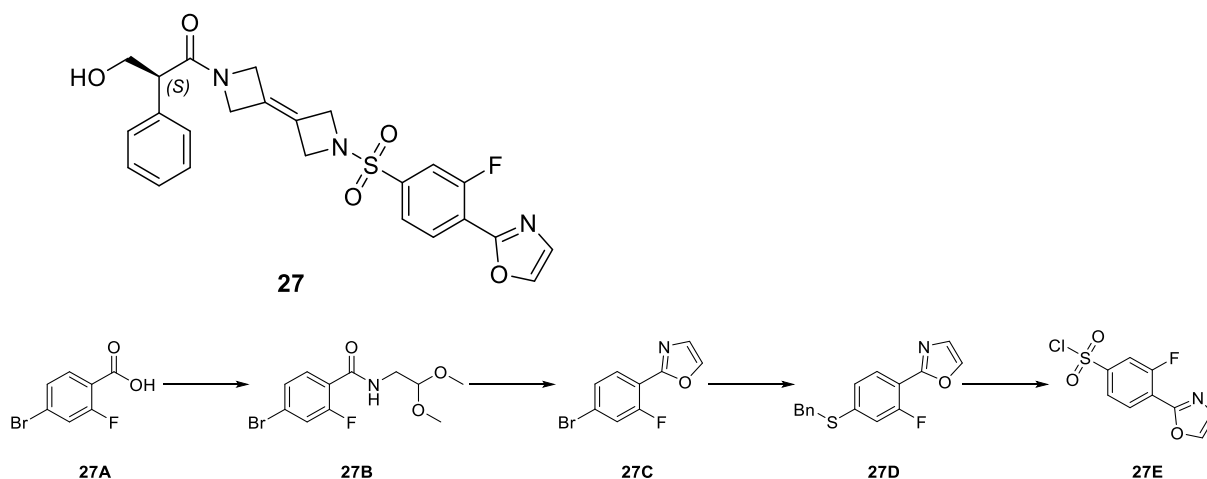


In step 10 of Example 1, 3-((tert-butyl-diphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-chlorophenyl)propionic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 26** of Example 26.

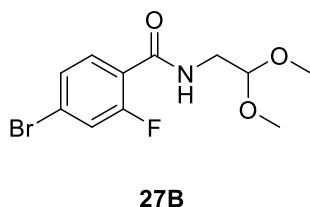
5 MS (ESI) m/z 504.1 ($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.36-7.24 (m, 6H), 7.07-7.05 (d, $J = 26.1$, 1H), 4.40-4.30 (m, 4H), 4.02-3.92 (m, 8H), 3.34 (s, 5H), 3.07-3.05 (m, 1H), 1.23 (s, 1H).

Example 27: preparation of *(S)*-1-(1'-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 27**):



Step 1: preparation of 4-bromo-*N*-(2,2-dimethoxyethyl)-2-fluorobenzamide (**compound 27B**):

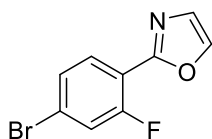


15 4-bromo-2-fluoro-benzoic acid (3 g, 13.70 mmol) was dissolved in dichloromethane solution (40 mL), and then added with *N,N*-diisopropylethylamine (3.53 g, 27.40 mmol) and *N,N*-carbonyl diimidazole (2.17 g, 15.07 mmol). The reaction was stirred at 25°C for 30 minutes. The aforementioned mixture was added with 2,2-dimethoxyethylamine (1.58 g, 15.07 mmol), and stirred at 25°C for another 4 hours. After the reaction was complete, it was separated and purified through a silica gel column to

20 obtain **compound 27B**.

MS (ESI) m/z 306.1 (M+H)⁺.

Step 2: preparation of 2-(4-bromo-2-fluorophenyl)oxazole (**compound 27C**):

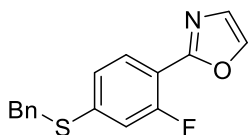


27C

4-bromo-*N*-(2,2-dimethoxyethyl)-2-fluoro-benzamide (2.1 g, 6.86 mmol) was added into polyphosphoric acid (20 mL) and reacted at 90°C for 5 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 27C**.

MS (ESI) m/z 243.0 (M+H)⁺.

Step 3: preparation of 2-(4-(benzylthio)-2-fluorophenyl)oxazole (**compound 27D**):

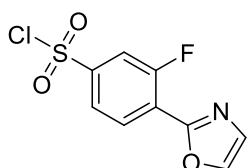


27D

Benzyl mercaptan (410.51 mg, 3.31 mmol), *N,N*-diisopropylethylamine (1.07 g, 8.26 mmol), tris(dibenzylideneacetone)dipalladium (342.09 mg, 330.52 μmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (382.74 mg, 661.04 μmol) were added into a solution of 2-(4-bromo-2-fluorophenyl)oxazole (0.8 g, 3.31 mmol) in 1,4-dioxane (10 mL), which were stirred at 90°C under the protection of nitrogen for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 27D**.

MS (ESI) m/z 286.3 (M+H)⁺.

Step 4: preparation of 3-fluoro-4-(oxazol-2-yl)benzenesulfonyl chloride (**compound 27E**):



27E

2-(4-benzylsulfanyl-2-fluoro-phenyl)oxazole (0.7 g, 2.45 mmol) was dissolved in a mixed solution of dichloromethane (10 mL), water (176.63 mg, 9.81 mmol) and glacial acetic acid (735.98 mg, 12.27 mmol), and then added dropwise with sulfonyl chloride (1.32 g, 9.81 mmol) at 0°C. The resulting mixed system was stirred at 20°C for 5 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 27E**.

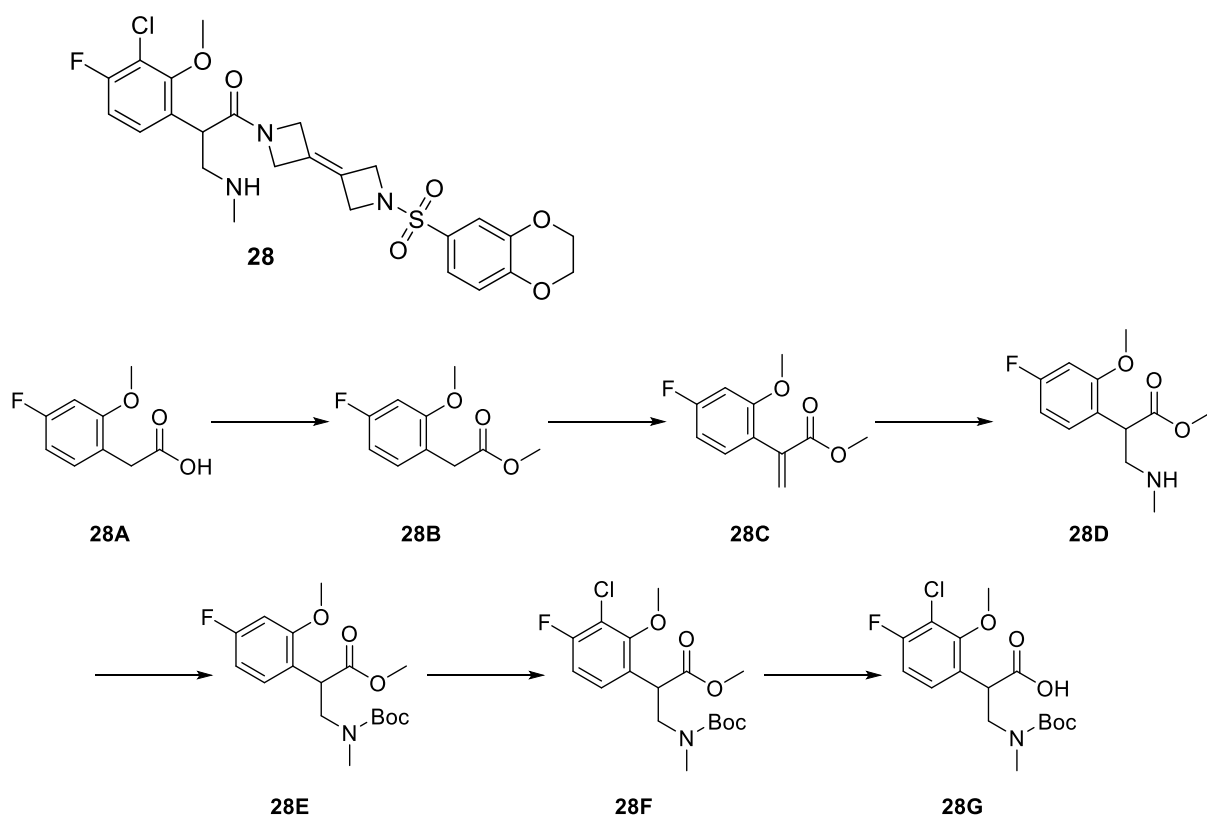
MS (ESI) m/z 262.0 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 3-fluoro-4-(oxazol-2-yl)benzenesulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 27** of Example 27.

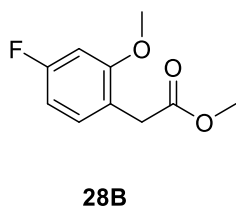
MS (ESI) m/z 484.1($M+H$)⁺.

- 5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (s, 1H), 8.37-8.35 (m, 1H), 8.02-8.01 (m, 1H), 7.74-7.73 (m, 1H), 7.53 (s, 1H), 7.27-7.21 (m, 5H), 4.81-4.79 (t, J = 0.8 Hz, 1H), 4.71-4.68 (d, J = 1.2 Hz, 1H), 4.35-4.21 (m, 7H), 3.88-3.87 (m, 1H), 3.62-3.58 (m, 1H), 3.48-3.42 (m, 1H).

10 **Example 28:** preparation of 2-(3-chloro-4-fluoro-2-methoxyphenyl)-1-(1'-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-(methylamino)propan-1-one (**compound 28**):



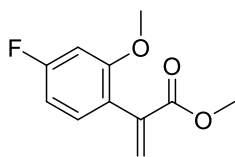
Step 1: preparation of methyl 2-(4-fluoro-2-methoxyphenyl)acetate (**compound 28B**):



- 15 2-(4-fluoro-2-methoxyphenyl)acetic acid (1.0 g, 5.43 mmol) was dissolved in anhydrous methanol (100 mL), and then slowly added with thionyl chloride (1.29 g, 10.8 mmol). The reaction solution was reacted at 70°C for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 28B**.

MS (ESI) m/z 199.1 (M+H)⁺.

Step 2: preparation of methyl 2-(4-fluoro-2-methoxyphenyl)acrylate (**compound 28C**):

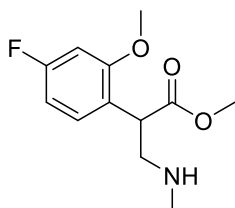


28C

- 5 Methyl 2-(4-fluoro-2-methoxyphenyl)acetate (900.0 mg, 4.54 mmol) was dissolved in *N,N*-dimethylformamide (100.0 mL), and then added with potassium carbonate (1.57 g, 11.4 mmol), paraformaldehyde (518.3 mg, 5.76 mmol) and tetrabutylammonium bromide (167.7 mg, 0.45 mmol), and the reaction solution was stirred at 60°C for 1 hour. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 28C**.

MS (ESI) m/z 211.1 (M+H)⁺.

- 10 **Step 3:** preparation of methyl 2-(4-fluoro-2-methoxyphenyl)-3-(methylamino)propionate (**compound 28D**):

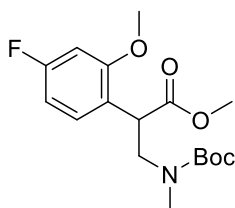


28D

- 15 Methyl 2-(4-fluoro-2-methoxyphenyl)acrylate (515.0 mg, 2.45 mmol) was dissolved in a solution of methylamine in tetrahydrofuran (20 mL), and the reaction solution was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 28D**.

MS (ESI) m/z 242.1 (M+H)⁺.

Step 4: preparation of methyl 3-(tert-butoxycarbonyl)(methylamino)-2-(4-fluoro-2-methoxyphenyl)propionate (**compound 28E**):



28E

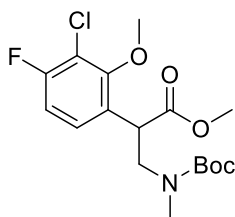
20

Methyl 2-(4-fluoro-2-methoxyphenyl)-3-(methylamino)propionate (406 mg, 1.68 mmol) was dissolved in dichloromethane (50 mL), and then added with triethylamine (340 mg, 3.37 mmol). The temperature of the reaction system was reduced to 0°C, the reaction system was slowly added with di-tert-butyl dicarbonate (440 mg, 2.02 mmol), and the reaction solution was stirred at room temperature for 16

hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (100 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 28E**.

5 MS (ESI) m/z 342.1 (M+H)⁺.

Step 5: preparation of methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-chloro-4-fluoro-2-methoxyphenyl)propionate (**compound 28F**):

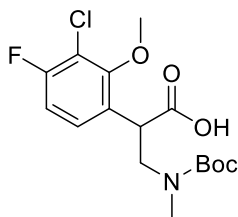


28F

10 Methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2-(4-fluoro-2-methoxyphenyl)propionate (393 mg, 1.15 mmol) was dissolved in *N,N*-dimethylformamide (100.0 mL), and then added with *N*-chlorosuccinimide (461.3 mg, 3.45 mmol). The reaction solution was reacted at room temperature for 16 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (100 mL*3). The organic phases were combined,
15 washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 28F**.

MS (ESI) m/z 376.1 (M+H)⁺.

Step 6: preparation of 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-chloro-4-fluoro-2-methoxyphenyl)propionic acid (**compound 28G**):



28G

Methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-chloro-4-fluoro-2-methoxyphenyl)propionate (302 mg, 0.81 mmol) was dissolved in tetrahydrofuran (50 mL) and water (50 mL), and then added with lithium hydroxide (38.6 g, 1.61 mmol). The reaction solution was reacted at room temperature for 16 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (100 mL*3). The organic phases were combined,
25 washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 28G**.

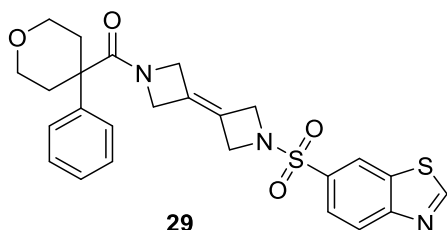
MS (ESI) m/z 362.1 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 2,3-dihydrobenzo[*b*][1,4]dioxin-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyl-diphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-chloro-4-fluoro-2-methoxyphenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 28** of Example 28.

MS (ESI) m/z 552.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.25-7.21 (m, 3H), 7.13-7.10 (d, *J* = 8.0 Hz, 1H), 7.04-7.02 (d, *J* = 8.0 Hz, 1H), 4.45-4.15 (m, 6H), 3.98 (s, 6H), 3.78 (s, 3H), 2.96-2.94 (d, *J* = 8.0 Hz, 1H), 2.20 (s, 2H), 1.41-0.82 (m, 4H).

Example 29: preparation of (1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)(4-phenyltetrahydro-2*H*-pyran-4-yl)methanone (**compound 29**):

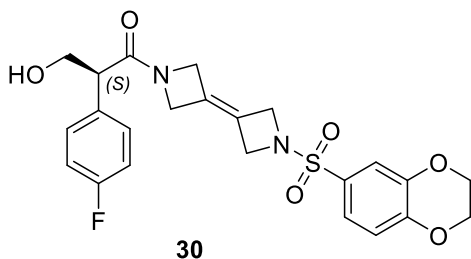


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyl-diphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 4-phenyltetrahydro-2*H*-pyran-4-carboxylic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 29** of Example 29.

MS (ESI) m/z 496.2 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.78-8.75 (d, *J* = 1.9 Hz, 1H), 8.32-8.29 (d, *J* = 8.5 Hz, 1H), 7.92-7.87 (m, 1H), 7.37-7.31 (m, 2H), 7.28-7.19 (m, 3H), 4.31-4.16 (m, 6H), 3.97-3.87 (m, 2H), 3.71-3.67 (m, 2H), 3.56-3.44 (m, 2H), 2.17-2.07 (m, 2H), 1.83-1.76 (m, 2H).

Example 30: preparation of (*S*)-1-(1'-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 30**):



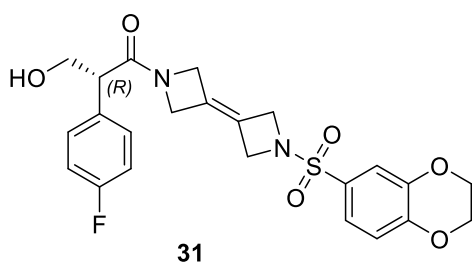
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by

2,3-dihydrobenzo[*b*][1,4]dioxin-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by (*S*)-2-(4-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 30** of Example 30.

5 MS (ESI) *m/z* 475.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.34-7.24 (m, 4H), 7.14-7.10 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 4.83-4.81 (m, 1H), 4.31-4.30 (m, 5H), 4.00-3.85 (m, 8H), 3.52-3.39 (m, 2H).

Example 31: preparation of (*R*)-1-(1'-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 31**):

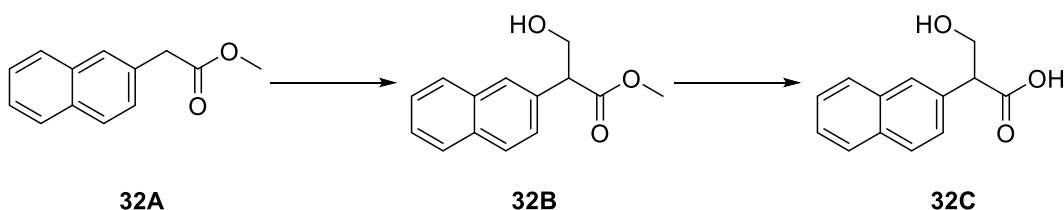
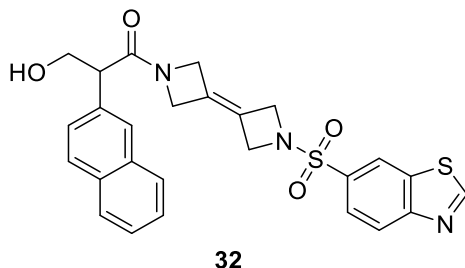


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 2,3-dihydrobenzo[*b*][1,4]dioxin-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by (*R*)-2-(4-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 31** of Example 31.

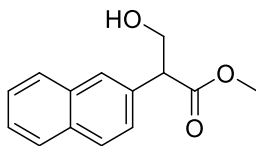
MS (ESI) *m/z* 475.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.34-7.24 (m, 4H), 7.14-7.10 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 4.83-4.81 (m, 1H), 4.31-4.30 (m, 5H), 4.00-3.85 (m, 8H), 3.52-3.39 (m, 2H).

Example 32: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-(naphthalene-2-yl)propan-1-one (**compound 32**):



Step 1: preparation of methyl 3-hydroxy-2-(naphthalene-2-yl)propionate (**compound 32B**):

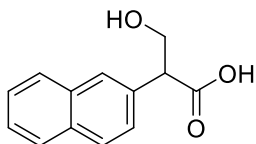


32B

Methyl 2-(naphthalene-2-yl)acetate (1.0 g, 4.99 mmol) and paraformaldehyde (449.9 mg, 4.99 mmol) were dissolved in dimethyl sulfoxide (40.0 mL), and then added with sodium methoxide (27.0 mg, 0.50 mmol). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (10 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 32B**.

MS (ESI) m/z 231.1 ($M+H$)⁺.

Step 2: preparation of 3-hydroxy-2-(naphthalene-2-yl)propionic acid (**compound 32C**):



32C

Methyl 3-hydroxy-2-(naphthalene-2-yl)propionate (260.0 mg, 1.13 mmol) was dissolved in a mixed solution of tetrahydrofuran (60.0 mL) and water (40.0 mL), and then added with sodium hydroxide (45.2 mg, 1.13 mmol), and the reaction solution was stirred at room temperature for 5 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (100 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. After concentration, it was directly used for the next step of reaction.

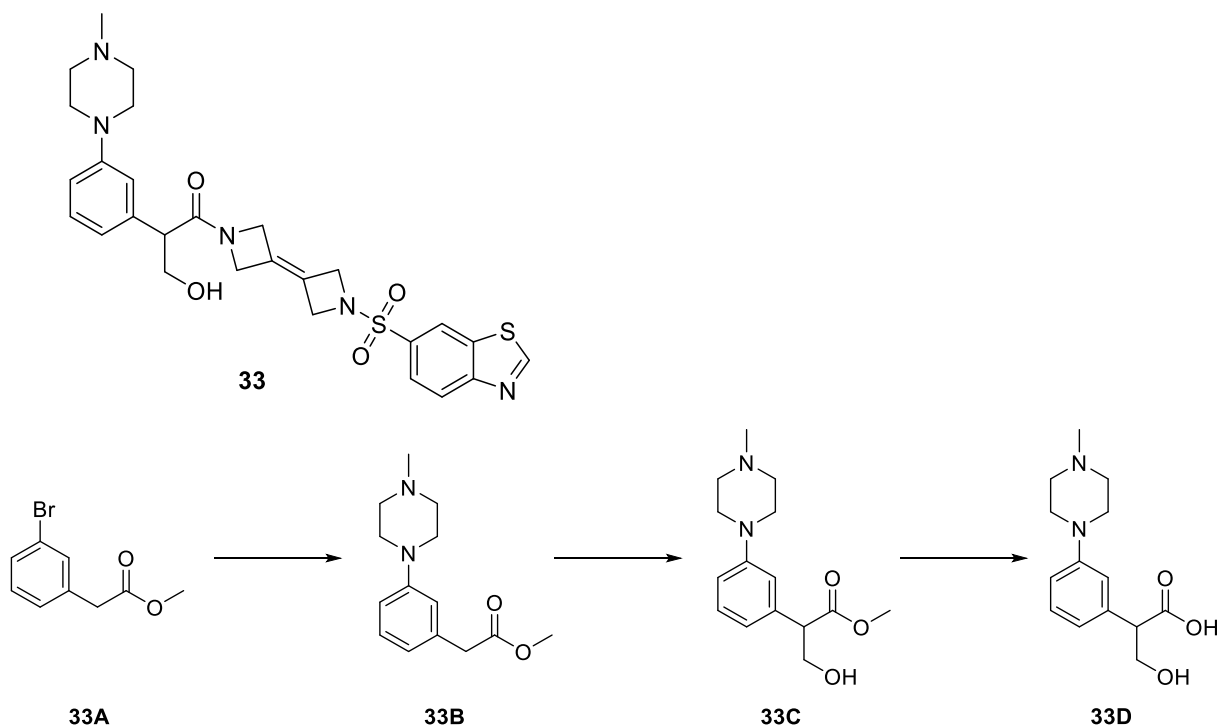
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(naphthalene-2-yl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 32** of Example 32.

MS (ESI) m/z 506.1 ($M+H$)⁺.

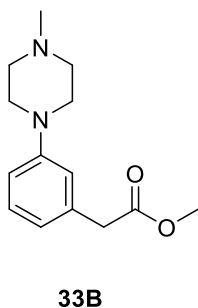
¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 1H), 8.78-8.77 (d, *J* = 4.0 Hz, 1H), 8.31-8.29 (d, *J* = 8.0 Hz, 1H), 7.92-7.90 (m, 1H), 7.85-7.80 (m, 3H), 7.72 (s, 1H), 7.47-7.44 (m, 2H), 7.40-7.33 (m, 1H), 4.80-4.78 (m, 1H), 4.72 (s, 1H), 4.34-4.26 (m, 6H), 4.19 (s, 1H), 3.95-3.92 (m, 1H), 3.77-3.74 (m, 1H), 3.57-3.53 (m, 1H).

Example 33: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl(1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-

2-(3-(4-methylpiperazin-1-yl)phenyl)propan-1-one (**compound 33**):



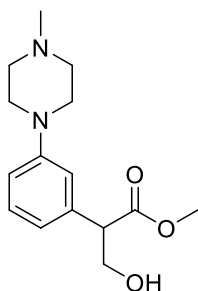
5 **Step 1:** preparation of methyl 2-(3-(4-methylpiperazin-1-yl)phenyl)acetate (**compound 33B**)



Methyl 2-(3-bromophenyl)acetate (5.0 g, 21.83 mmol), 1-methylpiperazine (3.3 g, 32.74 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (1.3 g, 2.18 mmol) and cesium carbonate (10.7 g, 32.74 mmol) were dissolved in toluene (100.0 mL), and then added with tris(dibenzylideneacetone)dipalladium (399.8 mg, 0.44 mmol). After the addition was completed, the reaction system was placed under a nitrogen protection environment, heated to 110°C, and stirred for 16 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (150.0 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 33B**.

MS (ESI) m/z 249.2 (M+H)⁺.

Step 2: preparation of methyl 3-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)propionate (**compound 33C**)

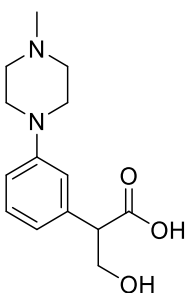


33C

Methyl 2-(3-(4-methylpiperazin-1-yl)phenyl)acetate (1.8 g, 7.25 mmol) and paraformaldehyde (685.6 mg, 7.61 mmol) were dissolved in dimethyl sulfoxide (90.0 mL), and then added with sodium methoxide (39.2 mg, 0.72 mmol). The reaction solution was reacted at 50°C for 4 hours. The reaction solution was diluted by adding water. The aqueous phase was extracted with dichloromethane (100 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 33C**.

MS (ESI) m/z 279.2 (M+H)⁺

Step 3: preparation of 3-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)propionic acid (**compound 33D**)



33D

Methyl 3-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)propionate (90.0 mg, 0.32 mmol) was dissolved in methanol (2.5 mL) and water (2.5 mL), and then added with sodium hydroxide (25.9 mg, 0.64 mmol), and the reaction solution was stirred at room temperature for 3 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, concentrated, and then used directly in the next step of reaction.

MS (ESI) m/z 265.2 (M+H)⁺.

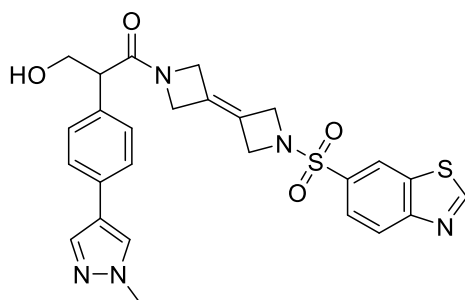
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 33** of Example 33.

MS (ESI) m/z 554.2 (M+H)⁺.

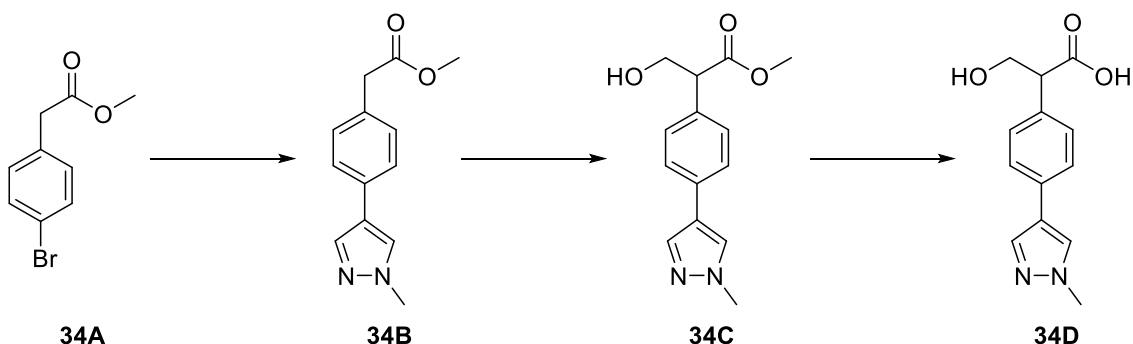
¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.81-8.80 (d, *J* = 1.7 Hz, 1H), 8.33-8.31 (d, *J* = 8.6 Hz, 1H), 7.5-7.94 (m, 1H), 7.11-7.07 (m, 1H), 6.78-6.76 (m, 2H), 6.64-6.62 (d, *J* = 7.6 Hz, 1H), 4.71-4.63

(m, 2H), 4.42-4.11 (m, 7H), 3.88-3.81 (m, 1H), 3.54-3.49 (m, 1H), 3.44-3.38 (m, 1H), 3.17-2.97 (m, 4H), 2.47-2.38 (m, 4H), 2.21 (s, 3H).

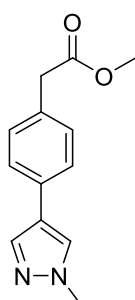
Example 34: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-(4-(1-methyl-1*H*-pyrazol-4-yl) phenyl)propan-1-one (**compound 34**):



34



Step 1: preparation of methyl 2-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)acetate (**compound 34B**)

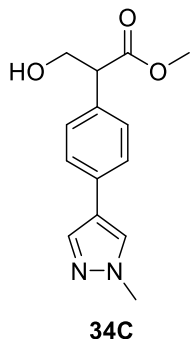


34B

- 10 Methyl 2-(4-bromophenyl)acetate (1.0 g, 4.37 mmol), (1-methyl-1*H*-pyrazol-4-yl)boronic acid (604.7 mg, 4.80 mmol) and potassium carbonate (1.2 g, 8.74 mmol) were dissolved in a mixed solution of dioxane and water (4:1, 20.0 mL), and then added with tetrakis(triphenylphosphine)palladium (504.5 mg, 0.44 mmol). After the addition was completed, the reaction system was placed under a nitrogen protection environment, heated to 80°C, and stirred for 16 hours. After the reaction was
- 15 complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (50.0 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 34B**.

MS (ESI) m/z 231.2 (M+H)⁺.

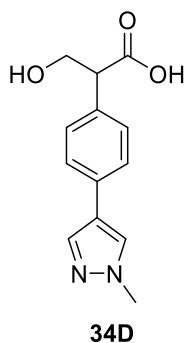
Step 2: preparation of methyl 3-hydroxy-2-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)propionate (**compound 34C**)



5 Methyl 2-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)acetate (800.0 mg, 3.47 mmol) and paraformaldehyde (313.0 mg, 3.47 mmol) were dissolved in dimethyl sulfoxide (50.0 mL), and then added with sodium methoxide (62.6 mg, 0.35 mmol). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (50 mL*3). The organic phases were combined, washed with a
10 saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 34C**.

MS (ESI) m/z 261.2 (M+H)⁺.

Step 3: preparation of 3-hydroxy-2-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)propionic acid (**compound 34D**)



15 Methyl 3-hydroxy-2-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)propionate (200.0 mg, 0.77 mmol) was dissolved in a mixed solution of methanol (6.0 mL) and water (4.0 mL), and then added with sodium hydroxide (61.5 mg, 1.54 mmol), and the reaction solution was stirred at room temperature for 16 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, concentrated, and then used directly in the next step of reaction.
20

MS (ESI) m/z 267.1 (M+H)⁺.

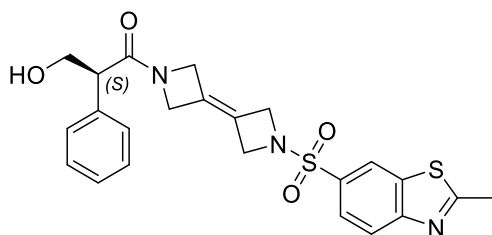
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyl)di(phenyl)silyl)oxy)-2-phenylpropionic acid was replaced by
25 3-hydroxy-2-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)propionic acid, and the same preparation method as

that of Example 1 was adopted to obtain **compound 34** of Example 34.

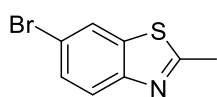
MS (ESI) m/z 536.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.81-8.80 (d, *J* = 1.6 Hz, 1H), 8.32-8.31 (d, *J* = 8.6 Hz, 1H), 8.06 (s, 1H), 7.95-7.92 (d, *J* = 8.6, 1H), 7.79 (s, 1H), 7.45-7.43 (d, *J* = 8.2 Hz, 2H), 7.20-7.18 (d, *J* = 8.2 Hz, 2H), 4.77-4.74 (t, *J* = 5.3 Hz, 1H), 4.68-4.65 (m, 1H), 4.44-4.12 (m, 7H), 3.90-3.81 (m, 4H), 3.60-3.54 (m, 1H), 3.49-3.40 (m, 1H).

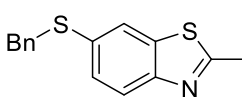
Example 35: preparation of *(S)*-3-hydroxy-1-(1'-((2-methylbenzo[*d*]thiazol-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinydene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 35**):



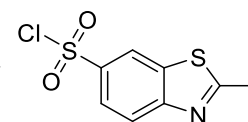
35



35A

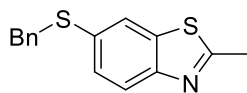


35B



35C

Step 1: preparation of 6-(benzylthio)-2-methylbenzo[*d*]thiazole (**compound 35B**)

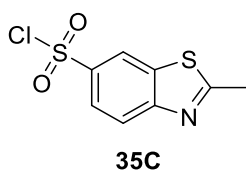


35B

6-bromo-2-methylbenzo[*d*]thiazole (2.0 g, 8.77 mmol), benzyl mercaptan (1.3 g, 10.52mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.5 g, 0.88 mmol) and *N,N*-diisopropylethylamine (3.4 g, 26.30 mmol) were dissolved in 1,4-dioxane (50.0 mL), and then added with tris(dibenzylideneacetone)dipalladium (401.4 mg, 0.44 mmol). After the addition was completed, the reaction system was placed under a nitrogen protection environment, heated to 100°C, and stirred for 16 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (150.0 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain compound **35B**.

MS (ESI) m/z 272.1 (M+H)⁺.

Step 2: preparation of 2-methylbenzo[*d*]thiazole-6-sulfonyl chloride (**compound 35C**)



6-(benzylthio)-2-methylbenzo[d]thiazole (1.0 g, 3.68 mmol) was dissolved in a mixed solution of acetonitrile (40.0 mL), acetic acid (1.5 mL) and water (1.0 mL), and then the reaction system was added with 1,3-dichloro-5,5-dimethylhydantoin (1.5 g, 7.37 mmol) at 0°C. After the addition was complete, the reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (50 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 35C**.

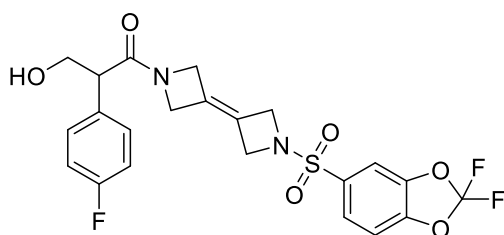
MS (ESI) m/z 248.0 (M+H)⁺.

- 10 In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 2-methylbenzo[d]thiazole-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 35** of Example 35.

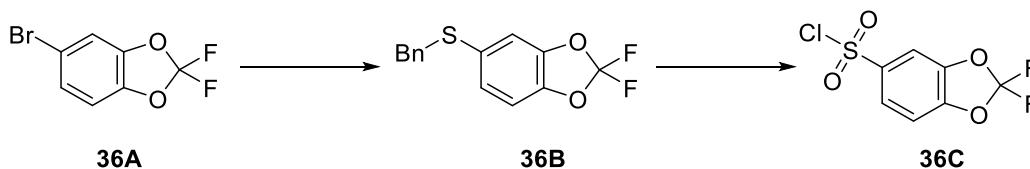
MS (ESI) m/z 470.1(M+H)⁺.

- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66-8.65 (d, J = 1.6 Hz, 1H), 8.15-8.13 (d, J = 8.5 Hz, 1H), 7.89-7.86 (d, J = 8.5, 1H), 7.29-7.19 (m, 5H), 4.79-4.76 (t, J = 5.2 Hz, 1H), 4.69-4.65 (m, 1H), 4.33-4.15 (m, 7H), 3.90-3.84 (m, 1H), 3.61-3.57 (m, 1H), 3.47-3.42 (m, 1H), 2.87 (s, 3H).

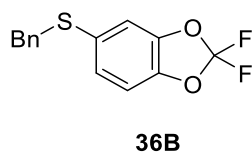
Example 36: preparation of 1-(1'-((2,2-difluorobenzo[d][1,3]dioxolan-5-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 36**):



20



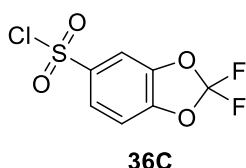
Step 1: preparation of 5-(benzylthio)-2,2-difluorobenzo[d][1,3]dioxolane (**compound 36B**)



5-bromo-2,2-difluoro-1,3-benzodioxolane (400 mg, 1.69 mmol) and benzyl mercaptan (280 mg, 2.25 mmol) were dissolved in dioxane (10 mL), and then added with sodium tert-butoxide (400.00 mg, 4.16 mmol), palladium acetate (40.00 mg, 178.57 μ mol) and 1,1'-binaphthyl-2,2'-bis(diphenylphosphine) (100 mg, 160.60 μ mol). After the addition was completed, the reaction system was placed under a nitrogen atmosphere and stirred at 100°C for 16 hours, and cooled to room temperature after the reaction was ended. The reaction solution was diluted by adding water, the aqueous phase was extracted with ethyl acetate (30.0 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 36B**.

MS (ESI) m/z 280.1(M+H)⁺.

Step 2: preparation of 2,2-difluorobenzo[d][1,3]dioxolane-5-sulfonyl chloride (**compound 36C**)



2,2-difluoro-5-phenylthio-1,3-benzodioxolane (270 mg, 963.29 μ mol) was dissolved in acetonitrile (20 mL), acetic acid (0.75 mL) and water (0.5 mL), and added with 5-dimethyl-imidazolidine-2,4-dione (380 mg, 1.93 mmol) at 0°C. After the addition was completed, the reaction system was placed under nitrogen atmosphere and stirred at room temperature for 2 hours. After the reaction was ended, the reaction solution was concentrated and adjusted to the pH value of 6-7 with a saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate (30.0 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 36C**.

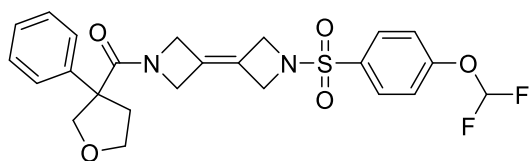
MS (ESI) m/z 257.0(M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 2,2-difluorobenzo[d][1,3]dioxolane-5-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyl)diphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 36** of Example 36.

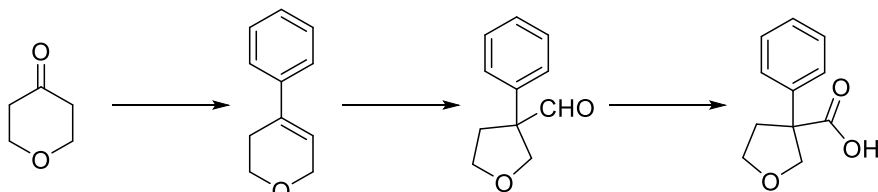
MS (ESI) m/z 497.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO- *d*₆) δ 7.92 (s, 1H), 7.74 - 7.68 (m, 2H), 7.31-7.28 (m, 2H), 7.11 (t, *J* = 8.8 Hz, 2H), 4.83 - 4.80 (m, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.38 - 4.19 (m, 7H), 3.87 - 3.81 (m, 1H), 3.66 - 3.63 (m, 1H), 3.47 - 3.42 (m, 1H).

Example 37: preparation of (1'-((4-(difluoromethoxy)phenyl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)(3-phenyltetrahydrofuran-3-yl)methanone (**compound 37**):



37



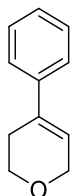
37A

37B

37C

37D

Step 1: preparation of 4-phenyl-3,6-dihydro-2*H*-pyran (**compound 37B**)

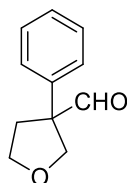


37B

- 5 An arylmagnesium bromide solution (2.8 N, 12.86 mL, 36 mmol) was slowly added into a solution of tetrahydro-4*H*-pyran-4-one (3.0 g, 29.97 mmol) in tetrahydrofuran (300 mL) at -78°C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 2 hours, and separated and purified through a silica gel column to obtain **compound 37B**.

MS (ESI) m/z 161.1 ($M+H$)⁺.

- 10 **Step 2:** preparation of 3-phenyltetrahydrofuran-3-carboxaldehyde (**compound 37C**)

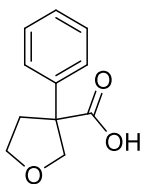


37C

- 15 4-phenyl-3,6-dihydro-2*H*-pyran (1 g, 6.24 mmol) and sodium carbonate (1.7 g, 16.04 mmol) were dissolved in dichloromethane (150 mL), added with *m*-chloroperoxybenzoic acid (2.4 g, 13.95 mmol) at 0°C, and then stirred at room temperature under nitrogen atmosphere for 3 hours. After the reaction was complete, the system was added with a saturated aqueous sodium carbonate solution (50 mL), and added with ethyl acetate (50 mL*3) until the reaction mixture is separated from the organic layer. The organic extract was dried over anhydrous magnesium sulfate, and separated and purified through a silica gel column to obtain **compound 37C**.

MS (ESI) m/z 177.1 ($M+H$)⁺.

- 20 **Step 3:** preparation of 3-phenyltetrahydrofuran-3-carboxylic acid (**compound 37D**)



37D

3-phenyltetrahydrofuran-3-carboxaldehyde (250 mg, 1.42 mmol) and 2-methylbut-2-ene (2.25 mL) were dissolved in n-butanol (45 mL) and 2-methylbut-2-ene (2.25 mL), and added with sodium chlorite (520 mg, 4.62 mmol) and potassium dihydrogen phosphate (440 mg, 3.24 mmol) at room temperature, and the resulting mixture was stirred at room temperature under nitrogen atmosphere for 0.5 hours. After the reaction was complete, it was extracted with ethyl acetate (10 mL*3), and the organic phases were combined. It was separated and purified through a silica gel column to obtain **compound 37D**.

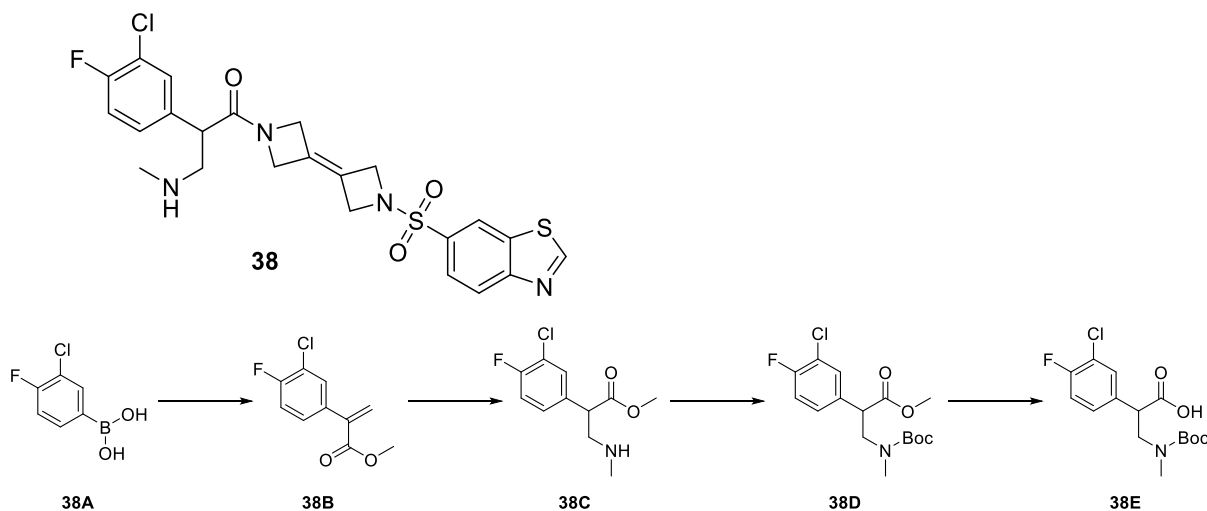
MS (ESI) m/z 193.1 (M+H)⁺.

In step 4 of Example 6, 3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-phenyltetrahydrofuran-3-carboxylic acid, and the same preparation method as that of Example 6 was adopted to obtain **compound 37** of Example 37.

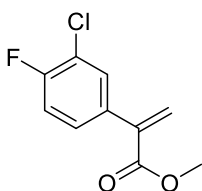
MS (ESI) m/z 491.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.88 - 7.84 (m, 2H), 7.63 - 7.21 (m, 8H), 4.27 - 4.17 (m, 7H), 3.99 (s, 2H), 3.83 - 3.77 (m, 3H), 2.60 - 2.55 (m, 1H), 2.23 - 2.16 (m, 1H).

Example 38: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(3-chloro-4-fluorophenyl)-3-(methylamino)propan-1-one (**compound 38**):



Step 1: preparation of methyl 2-(3-chloro-4-fluorophenyl)acrylate (**compound 38B**)

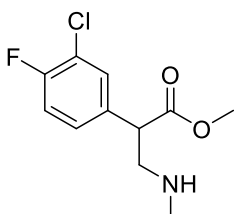


38B

(3-chloro-4-fluorophenyl)boronic acid (1.0 g, 5.74 mmol), methyl 2-bromoacrylate (860.2 mg, 32.74mmol), and potassium phosphate (2.2 g, 10.43 mmol) were dissolved in a mixed solution (25.0 mL) of dioxane and water (4:1), and then added with
 5 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (378.5 mg, 0.52 mmol). After the addition was completed, the reaction system was placed under a nitrogen protection environment, heated to 80°C, and stirred for 16 hours. After the reaction was complete, the reaction solution was diluted with water. The aqueous phase was extracted with ethyl acetate (150.0 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and
 10 purified through a silica gel column to obtain **compound 38B**.

MS (ESI) m/z 215.2 (M+H)⁺.

Step 2: preparation of methyl 2-(3-chloro-4-fluorophenyl)-3-(methylamino)propionate (**compound 38C**)

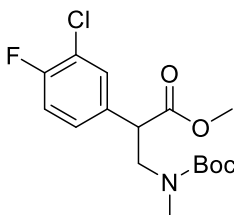


38C

15 Methyl 2-(3-chloro-4-fluorophenyl)acrylate (395.0 mg, 1.84 mmol) was dissolved in a solution of methylamine in tetrahydrofuran (8.0 mL). The reaction solution was reacted at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 38C**.

MS (ESI) m/z 246.1 (M+H)⁺.

20 **Step 3:** preparation of methyl 3-(tert-butoxycarbonyl)(methylamino)-2-(3-chloro-4-fluorophenyl)propionate (**compound 38D**)



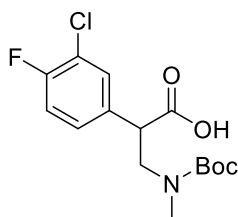
38D

2-(3-chloro-4-fluorophenyl)-3-(methylamino)propionate (276.0 mg, 1.12 mmol), *N,N*-dimethylamino

pyridine (13.7 mg, 0.11 mmol) and triethylamine (227.4 mg, 2.25 mmol) were dissolved in dichloromethane (5 mL), and then added with di-tert-butyl dicarbonate (244.9 mg, 1.12 mmol), and the reaction solution was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 38D**.

5 MS (ESI) m/z 346.1 (M+H)⁺.

Step 4: preparation of 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-chloro-4-fluorophenyl)propionic acid (**compound 38E**)



38E

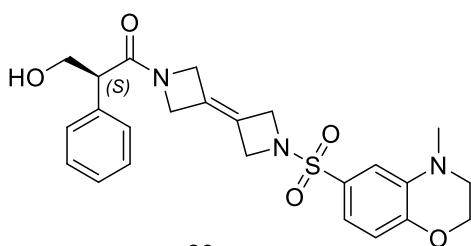
10 Methyl 3-(tert-butoxycarbonyl)(methyl)amino)-2-(3-chloro-4-fluorophenyl)propionate (245.0 mg, 0.71 mmol) was dissolved in a mixed solution of methanol (5.0 mL) and water (5.0 mL), and then added with lithium hydroxide monohydrate (59.5 mg, 1.42 mmol). The reaction solution was stirred at room temperature for 3 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (100 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. it was
15 concentrated to obtain a white solid compound, which was directly used in the next step of reaction.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by
20 3-((tert-butoxycarbonyl)(methyl)amino)-2-(3-chloro-4-fluorophenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 38** of Example 38.

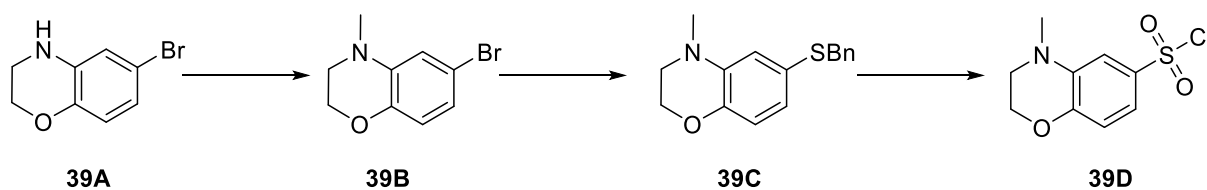
MS (ESI) m/z 521.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.69 (s, 1H), 8.82 (s, 1H), 8.37-8.31 (d, *J* = 8.5 Hz, 1H), 7.98-7.91 (d, *J* = 8.5 Hz, 1H), 7.49-7.42 (d, *J* = 8.5 Hz, 1H), 7.37-7.21 (m, 2H), 4.70-4.61 (m, 1H), 4.43-4.13 (m, 7H), 3.73-3.64 (t, *J* = 7.0 Hz, 1H), 3.00-2.89 (m, 1H), 2.64-2.55 (m, 2H), 2.21 (s, 3H).

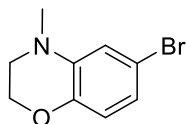
25 **Example 39:** preparation of (*S*)-3-hydroxy-1-(1'-((4-methyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 39**):



39



Step 1: preparation of 6-bromo-4-methyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazine (**compound 39B**)

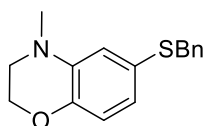


39B

6-bromo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine (0.5 g, 2.34 mmol), paraformaldehyde (140.3 mg, 4.67 mmol) and sodium cyanoborohydride (234.8 mg, 3.74 mmol) were dissolved in acetonitrile solution (30 mL). After the addition was completed, the reaction system was placed and stirred at room temperature for 0.5 hours, and then added with glacial acetic acid (0.5 mL). After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (60 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 39B**.

MS (ESI) m/z 228.0 (M+H)⁺.

Step 2: preparation of 6-(benzylthio)-4-methyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazine (**compound 39C**)

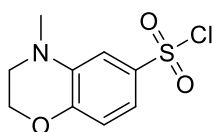


39C

6-bromo-4-methyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazine (0.45 g, 1.77 mmol), benzyl mercaptan (0.26 g, 3.54 mmol), tris(dibenzylideneacetone)dipalladium (0.09 g, 0.09 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.1 g, 0.18 mmol) and *N,N*-diisopropylethylamine (686 mg, 5.31 mmol) were dissolved in a mixed solution of methanol (7.0 mL) and water (3.0 mL). After the addition was completed, the reaction system was placed and stirred at room temperature overnight. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 39C**.

MS (ESI) m/z 272.3(M+H)⁺.

Step 3: preparation of 4-methyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-6-sulfonyl chloride (**compound 39D**)



39D

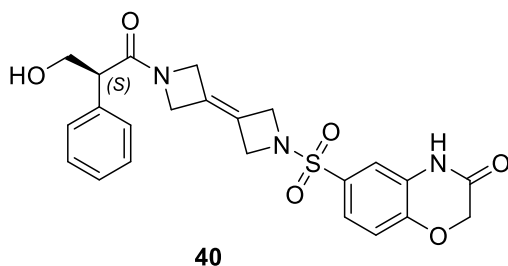
6-(benzylthio)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (375 mg, 1.38 mmol) was added into a mixed solvent (acetonitrile:acetic acid:water = 40:1.5:1) (25 mL), and added with 1,3-dichloro-5,5-dimethylhydantoin (545 mg, 2.76 mmol) under stirring at 0°C. Then it was stirred at room temperature for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 39D**.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 39** of Example 39.

MS (ESI) *m/z* 470.2(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.29-7.21 (m, 5H), 7.01-6.99 (m, 1H), 6.92-6.87 (m, 2H), 4.79-4.76 (t, *J* = 10.8 Hz, 1H), 4.73-4.70 (t, *J* = 13.2 Hz, 1H), 4.31-4.24 (m, 9H), 3.89-3.88 (m, 1H), 3.62-3.60 (m, 1H), 3.48-3.47 (m, 1H), 3.28 (s, 2H), 2.89 (s, 3H).

Example 40: preparation of (S)-6-((1'-(3-hydroxy-2-phenylpropionyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)sulfonyl)-2*H*-benzo[*b*][1,4]oxazine-3(4*H*)-one (**compound 40**):

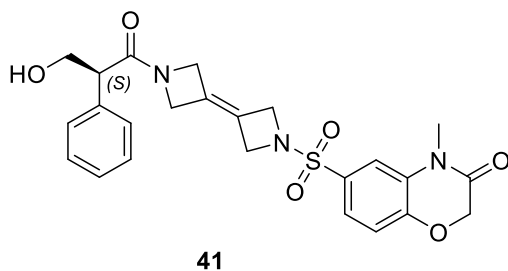


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 40** of Example 40.

MS (ESI) *m/z* 470.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.92 (s, 1H), 7.38-7.17 (m, 8H), 4.81-4.79 (m, 1H), 4.78-4.70 (m, 3H), 4.29-4.26 (m, 7H), 3.91-3.87 (m, 1H), 3.63-3.61 (m, 1H), 3.46-3.42 (m, 1H).

Example 41: preparation of (S)-6-((1'-(3-hydroxy-2-phenylpropionyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)sulfonyl)-4-methyl-2*H*-benzo[*b*][1,4]oxazine-3(4*H*)-one (**compound 41**):



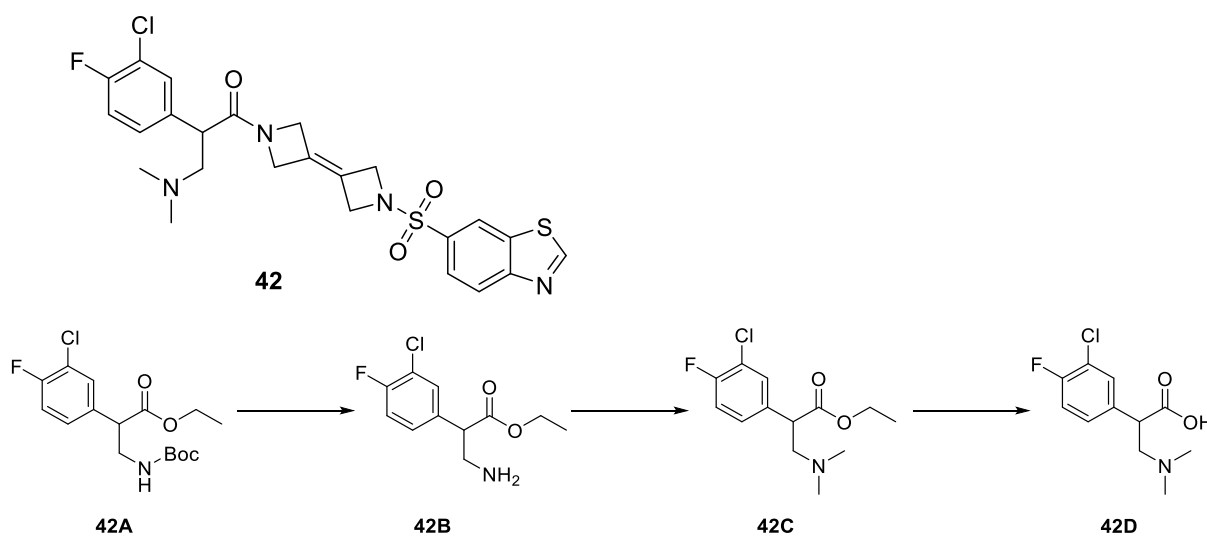
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by

4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 41** of Example 41.

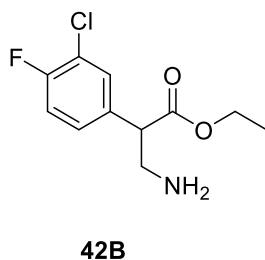
MS (ESI) m/z 484.2(M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.48-7.46 (d, 2H), 7.39 (s, 1H), 7.30-7.23 (m, 6 H), 4.81-4.70 (m, 4H), 4.31-4.19 (m, 8H), 3.91-3.85 (m, 1H), 3.63-3.60 (m, 1H), 3.51-3.43 (m, 2H).

Example 42: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(3-chloro-4-fluorophenyl)-3-(dimethylamino)propan-1-one (**compound 42**):



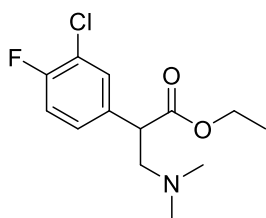
Step 1: preparation of ethyl 3-amino-2-(3-chloro-4-fluorophenyl)propionate (**compound 42B**)



Ethyl 3-(tert-butoxycarbonylamino)-2-(3-chloro-4-fluorophenyl)propionate (1 g, 2.89 mmol) was dissolved in hydrochloric acid-1,4-dioxane (200 mL), and then the reaction system was placed and stirred at room temperature under nitrogen atmosphere for 6 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 42B**.

MS (ESI) m/z 246.1 (M+H)⁺.

Step 2: preparation of ethyl 2-(3-chloro-4-fluorophenyl)-3-(dimethylamino)propionate (**compound 42C**)

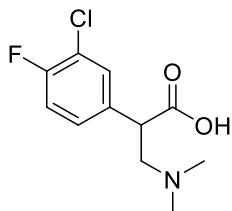


42C

Ethyl 3-amino-2-(3-chloro-4-fluorophenyl)propionate (801 mg, 3.26 mmol) was dissolved in methanol (30 mL), and added with *N,N*-diisopropylethylamine (842.74 mg, 6.52 mmol) and paraformaldehyde (587.39 mg, 6.52 mmol) at room temperature. After the addition was completed, the reaction system was placed under nitrogen atmosphere and stirred at 25°C for 6 hours. After the reaction was ended, it was separated and purified through a silica gel column to obtain **compound 42C**.

MS (ESI) m/z 274.1 (M+H)⁺.

Step 3: preparation of 2-(3-chloro-4-fluorophenyl)-3-(dimethylamino)propionic acid (**compound 42D**)



42D

Ethyl 2-(3-chloro-4-fluorophenyl)-3-(dimethylamino)propionate (391 mg, 1.43 mmol) was dissolved in ethanol (7 mL) and water (7 mL), and added with lithium hydroxide (119.99 mg, 2.86 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at 50°C under nitrogen atmosphere for 16 hours. After the reaction was ended, it was separated and purified through a silica gel column to obtain **compound 42D**.

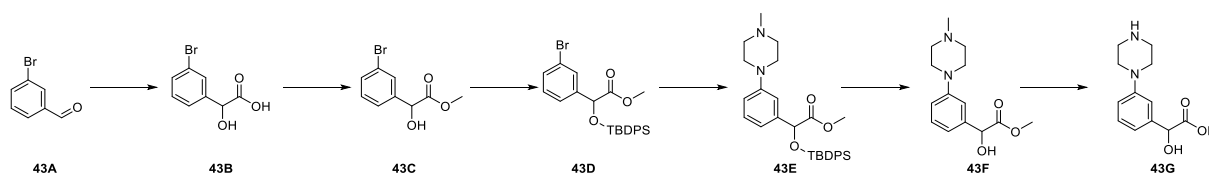
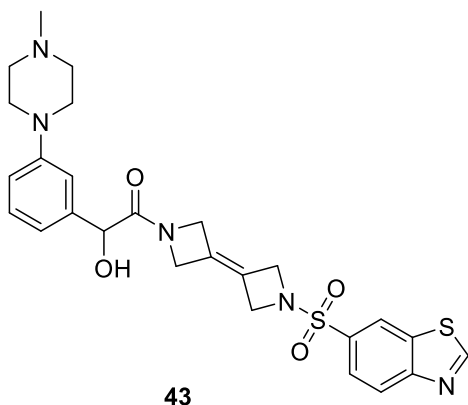
MS (ESI) m/z 246.2 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(3-chloro-4-fluorophenyl)-3-(dimethylamino)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 42** of Example 42.

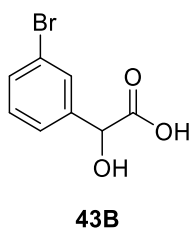
MS (ESI) m/z 535.1 (M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.82 (s, 1H), 8.35-8.33 (d, *J* = 8.5 Hz, 1H), 7.96-7.94 (d, *J* = 8.5 Hz, 1H), 7.49-7.47 (d, *J* = 7.1 Hz, 1H), 7.33-7.29 (m, 2H), 4.68-4.65 (d, *J* = 13.2 Hz, 1H), 4.48 - 4.15 (m, 7H), 3.74 - 3.71 (m, 1H), 2.78 - 2.67 (m, 1H), 2.37-2.33 (m, 1H), 2.09 (s, 6H).

Example 43: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)ethan-1-one (**compound 43**):



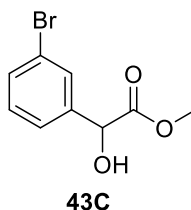
Step 1: preparation of 2-(3-bromophenyl)-2-hydroxyacetic acid (compound 43B)



- 5 3-bromobenzaldehyde (1.85 g, 10.0 mmol) was added into tetrahydrofuran (40 mL), and the solution was added with trimethylsilyl cyanide (1.1 g, 11.0 mmol) and added dropwise with 1 drop of 1N solution of tetrabutylammonium fluoride in tetrahydrofuran. The reaction solution was stirred at room temperature for 1 hour, and then subjected to rotary evaporation under reduced pressure to remove the solvent. The residual oil was added with 6N hydrochloric acid aqueous solution (10 mL), and heated to
- 10 reflux for 3 hours. The reaction mixture was cooled to 0°C and added dropwise with 10N sodium hydroxide solution to adjust pH to 1. After the reaction was complete, the mixture was extracted with ethyl acetate (60 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 43B**.

- 15 MS (ESI)m/z 230.1 (M-H)⁺.

Step 2: preparation of methyl 2-(3-bromophenyl)-2-hydroxyacetate (compound 43C)

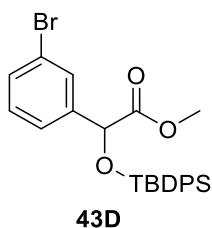


(3-bromophenyl)glycolic acid (500 mg, 2.16 mmol) was added into methanol (10 mL), thionyl chloride (773 mg, 6.49 mmol) was added dropwise into the reaction solution at room temperature, and after the

dropwise addition was completed, the reaction system was then placed and stirred at 60°C for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 43C**.

MS (ESI)m/z 268.1 (M+Na)⁺.

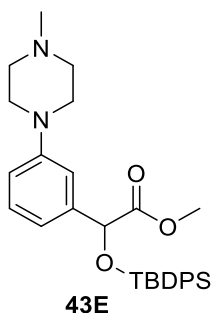
- 5 **Step 3:** preparation of methyl 2-(3-bromophenyl)-2-((tert-butyldiphenylsilyl)oxy)acetate (**compound 43D**)



- 10 Methyl 2-(3-bromophenyl)-2-hydroxyacetate (400 mg, 1.63 mmol), tert-butyldichlorodiphenylsilane (539 mg, 1.96 mmol), and imidazole (278 mg, 4.08 mmol) were added into tetrahydrofuran (8 mL), and stirred at 40°C for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 43D**.

MS (ESI)m/z 507.2 (M+Na)⁺.

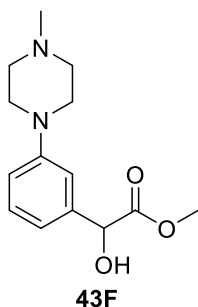
Step 4: preparation of methyl 2-((tert-butyldiphenylsilyl)oxy)-2-(3-(4-methylpiperazin-1-yl)phenyl)acetate (**compound 43E**)



- 15 Methyl 2-(3-bromophenyl)-2-((tert-butyldiphenylsilyl)oxy)acetate (400 mg, 0.83 mmol), 1-methylpiperazine (124 mg, 1.24 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (48 mg, 0.08 mmol), tris(dibenzylideneacetone)dipalladium (43 mg, 0.04 mmol) and cesium carbonate (540 mg, 1.65 mmol) were added into 1,4-dioxane (10 mL), and after being replaced with nitrogen for three times, it was stirred at 100°C overnight. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 43E**.

MS (ESI)m/z 542.6 (M+Na)⁺.

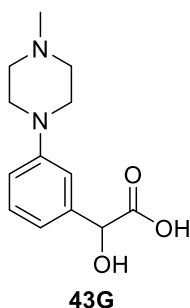
Step 5: preparation of methyl 2-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)acetate (**compound 43F**)



Methyl 2-((tert-butylidiphenylsilyl)oxy)-2-(3-(4-methylpiperazin-1-yl)phenyl)acetate (350 mg, 0.74 mmol) was dissolved in tetrahydrofuran (10 mL), and added with tetrabutylammonium fluoride (386 mg, 1.48 mmol), and the reaction system was placed and stirred at 50°C overnight. After the reaction was complete, the product was diluted by adding 50 mL of water, and extracted with ethyl acetate (50 mL*3) and water, and the organic phases were combined, dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 43F**.

MS (ESI)m/z 256.3 (M+H)⁺.

Step 6: preparation of 2-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)acetic acid (**compound 43G**)



Methyl 2-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)acetate (150 mg, 0.56 mmol) and sodium hydroxide (45 mg, 1.12 mmol) were dissolved in a mixed solution of methanol (3 mL) and water (3 mL), and then the reaction system was placed and stirred at 25°C for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 43G**.

MS (ESI) m/z 249.2(M-H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butylidiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-hydroxy-2-(3-(4-methylpiperazin-1-yl)phenyl)acetic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 43** of Example 43.

MS (ESI) m/z 540.2(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.80 - 8.79 (d, *J* = 1.6 Hz, 1H), 8.34-8.32 (d, *J* = 8.4 Hz, 1H), 7.95-7.92 (m, 1H), 7.14-7.10 (t, *J* = 15.6 Hz, 1H), 6.86-6.69 (m, 3H), 5.69-5.67 (d, *J* = 5.2 Hz, 1H), 4.93-4.92 (d, *J* = 5.6 Hz, 1H), 4.62-4.22 (m, 8H), 3.09-3.06 (t, *J* = 10 Hz, 4H), 2.43-2.41 (t, *J* = 9.6 Hz, 4H), 2.21 (s, 3H).

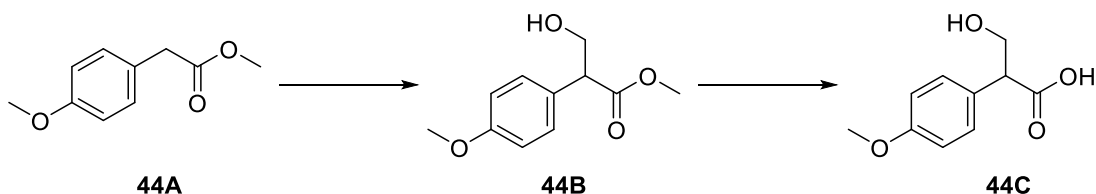
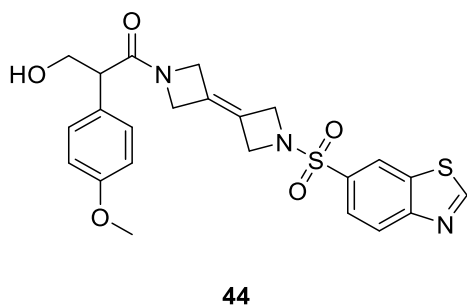
Example

44:

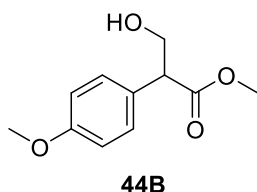
preparation

of

1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-(4-methoxyphenyl)propan-1-one (**compound 44**):



5 **Step 1:** preparation of methyl 3-hydroxy-2-(4-methoxyphenyl)propionate (**compound 44B**)

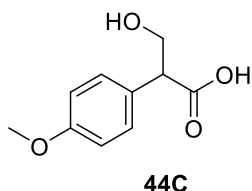


Methyl 2-(4-methoxyphenyl)acetate (1.0 g, 5.55 mmol), paraformaldehyde (524.4 mg, 5.83 mmol) and sodium methoxide (15 mg, 0.28 mmol) were dissolved in a dimethyl sulfoxide solution (10 mL). After the addition was completed, the reaction system was placed and stirred at room temperature for 3 hours.

10 After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 44B**.

MS (ESI) *m/z* 211.0 (M+H)⁺.

Step 2: preparation of 3-hydroxy-2-(4-methoxyphenyl)propionic acid (**compound 44C**)



15 Methyl 3-hydroxy-2-(4-methoxyphenyl)propionate (0.49 g, 2.33 mmol) and lithium hydroxide monohydrate (0.2 g, 4.66 mmol) were dissolved in a mixed solution of methanol (7.0 mL) and water (3.0 mL). After the addition was completed, the reaction system was placed and stirred at room temperature overnight. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 44C**.

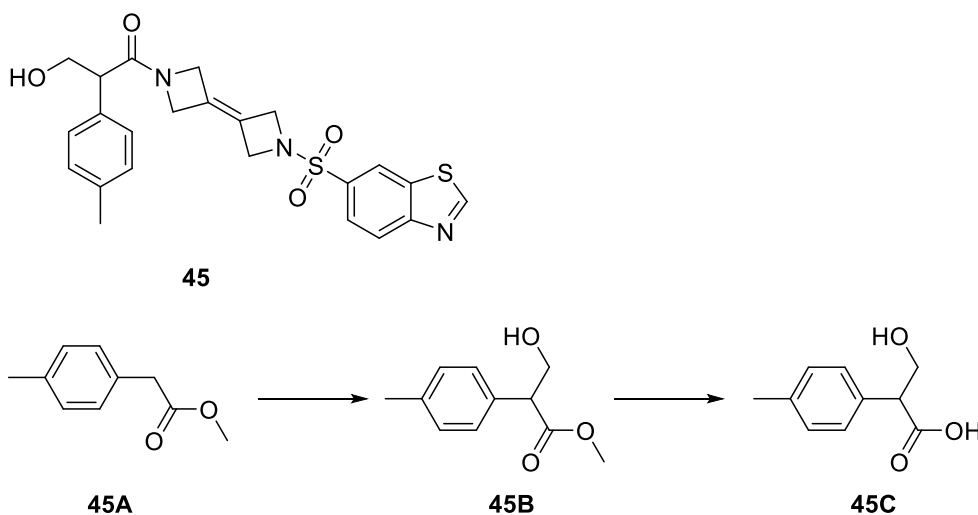
20 MS (ESI) *m/z* 197.0(M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butylidiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(4-methoxyphenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 44** of Example 44.

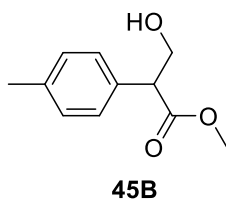
MS (ESI) m/z 486.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.81-8.80 (d, *J* = 2 Hz, 1H), 8.34-8.32 (d, *J* = 8.8 Hz, 1H), 7.95-7.92 (m, 1H), 7.14-7.12 (d, *J* = 8.8 Hz, 2H), 6.83-6.81 (d, *J* = 8.8 Hz, 2H), 4.73-4.63 (m, 2H), 4.34-4.23 (m, 6H), 3.83-3.80 (m, 1H), 3.69 (s, 3H), 3.54-3.50 (m, 1H), 3.41-3.37 (m, 2H).

Example 45: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-(*p*-tolyl)propan-1-one (**compound 45**):



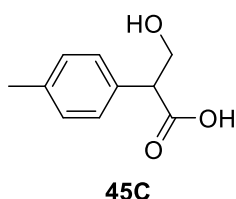
Step 1: preparation of methyl 3-hydroxy-2-(*p*-tolyl)propionate (**compound 45B**)



Methyl 2-(*p*-tolyl)acetate (0.5 g, 3.05 mmol) and paraformaldehyde (287.8 mg, 3.20 mmol) were dissolved in dimethyl sulfoxide (2.0 mL), and then added with sodium methoxide (8.2 mg, 0.31 mmol). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 45B**.

MS (ESI) m/z 195.1 (M+H)⁺.

Step 2: preparation of 3-hydroxy-2-(*p*-tolyl)propionic acid (**compound 45C**)



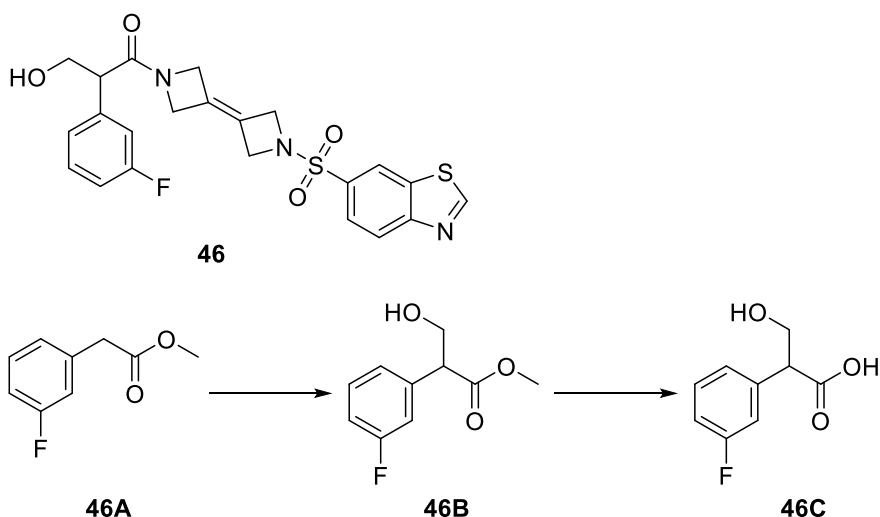
Methyl 2-(p-tolyl)acetate (380.0 mg, 1.96 mmol) was dissolved in a mixed solution of methanol (9.0 mL) and water (6.0 mL), and then added with sodium hydroxide (156.5 mg, 3.91 mmol), and the reaction solution was stirred at 25°C for 16 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (50 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. It was concentrated, and directly used in the next step of reaction.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(p-tolyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 45** of Example 45.

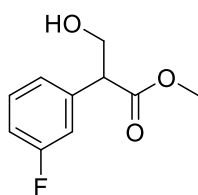
MS (ESI) m/z 470.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.81 (s, 1H), 8.34-8.32 (d, J = 9.1 Hz, 1H), 7.95-7.93 (d, J = 8.4 Hz, 1H), 7.09-7.08 (m, 4H), 4.73 -4.60 (m, 2H), 4.34 - 4.07 (m, 7H), 3.85-3.84(m, 1H), 3.54-3.52 (m, 1 H), 3.40- 3.38 (m, 1H), 2.23 (s, 3H).

Example 46: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(3-fluorophenyl)-3-hydroxypropan-1-one (**compound 46**):



Step 1: preparation of methyl 2-(3-fluorophenyl)-3-hydroxypropionate (**compound 46B**)

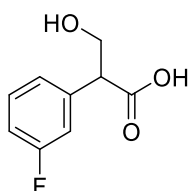


46B

Methyl 2-(3-fluorophenyl)acetate (1.0 g, 5.95 mmol) was dissolved in dimethyl sulfoxide (10 mL), and then added with sodium methoxide (100 mg, 1.85 mmol) and paraformaldehyde (535 mg, 5.94 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at room temperature under nitrogen atmosphere for 3 hours. The reaction solution was diluted by adding water, the aqueous phase was extracted with ethyl acetate (10.0 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 46B**.

MS (ESI) m/z 199.2 (M+H)⁺.

Step 2: preparation of 2-(3-fluorophenyl)-3-hydroxypropionic acid (compound 46C)



46C

Methyl 2-(3-fluorophenyl)-3-hydroxypropionate (610 mg, 3.08 mmol) was dissolved in methanol (6 mL) and water (6 mL), and added with lithium hydroxide (650 mg, 27.14 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at 60°C under nitrogen atmosphere for 3 hours. After the reaction was completed, the reaction solution was concentrated and adjusted to the pH value of 3-4 with 1N hydrochloric acid solution. The aqueous phase was extracted with ethyl acetate (10.0 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. It was separated and purified through a silica gel column to obtain **compound 46C**.

MS (ESI) m/z 183.1 (M-H)⁻.

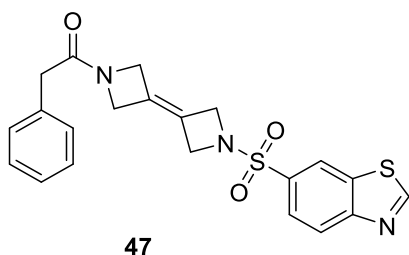
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(3-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 46** of Example 46.

MS (ESI) m/z 474.1(M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.81-8.80 (m, 1H), 8.34 - 8.32 (m, 1H), 7.95-7.93 (m, 1H), 7.34-7.28 (m, 1H), 7.09-7.03 (m, 3H), 4.38-4.16 (m, 8H), 3.86 - 3.81 (m, 1H), 3.66-3.58 (m, 2H), 3.51- 3.44 (m, 1H).

Example 47: preparation of

1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylethan-1-one (**compound 47**):

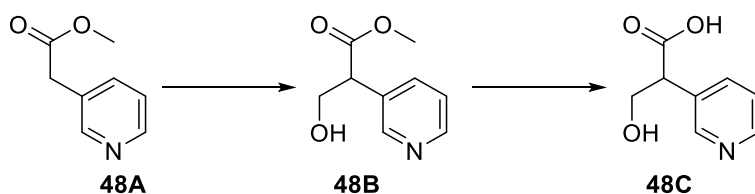
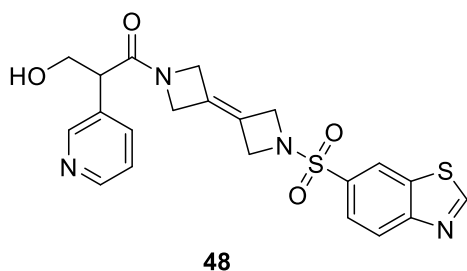


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butylidiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by phenylacetic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 47** of Example 47.

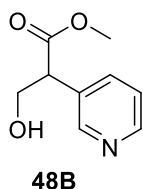
MS (ESI) *m/z* 426.1(*M*+*H*)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.69 (s, 1H), 8.82 (s, 1H), 8.35-8.33 (d, *J*=8.0 Hz, 1H), 7.96-7.94 (d, *J*=8.0 Hz, 1H), 7.27-7.15 (m, 5H), 4.54-4.22 (m, 8H), 3.44 (s, 2H).

Example 48: preparation of 1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-(pyridin-3-yl)propan-1-one (**compound 48**):



Step 1: preparation of methyl 3-hydroxy-2-(pyridin-3-yl)propionate (**compound 48B**)

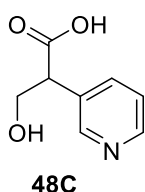


Methyl 2-(3-pyridyl)acetate (1.0 g, 6.62 mmol) was dissolved in dimethyl sulfoxide (10 mL), and then added with sodium methoxide (120 mg, 666.67 μmol) and paraformaldehyde (600 mg, 6.67 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at room

temperature under nitrogen atmosphere for 3 hours. The reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (30.0 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. It was separated and purified through a silica gel column to obtain **compound 48B**.

5 MS (ESI) m/z 182.1 (M+H)⁺.

Step 2: preparation of 3-hydroxy-2-(pyridin-3-yl)propionic acid (**compound 48C**)



Methyl 3-hydroxy-2-(2-pyridyl)propionate (140 mg, 772.68 μ mol) was dissolved in a mixed solution of methanol (2 mL), water (2 mL) and tetrahydrofuran (2 mL), and added with lithium hydroxide (350 mg, 8.33 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at 60°C under nitrogen atmosphere for 3 hours. After the reaction was ended, the reaction solution was concentrated and adjusted to pH 3-4 with 1N hydrochloric acid solution, the aqueous phase was extracted with ethyl acetate (10.0 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. It was separated and purified through a silica gel column to obtain **compound 48C**.

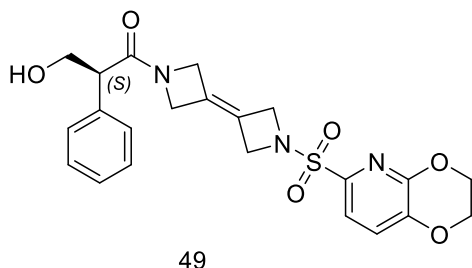
MS (ESI) m/z 168.1 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyl-diphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(pyridin-3-yl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 48** of Example 48.

MS (ESI) m/z 457.1(M+H)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.81- 8.79 (m, 1H), 8.43- 8.42(m, 2H), 8.37-8.32 (m, 1H), 7.96 - 7.93 (m, 1H), 7.68 -7.66 (m, 1H), 7.32 - 7.28 (m, 1H), 4.91 - 4.88 (m, 1H), 4.75 - 4.67 (m, 1H), 4.44 - 4.17 (m, 7H), 3.88 - 3.82 (m, 1H), 3.68 - 3.64 (m, 1H), 3.53 - 3.48 (m, 1H).

Example 49: preparation of (*S*)-1-(1'-((2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidiny]idene)-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 49**):

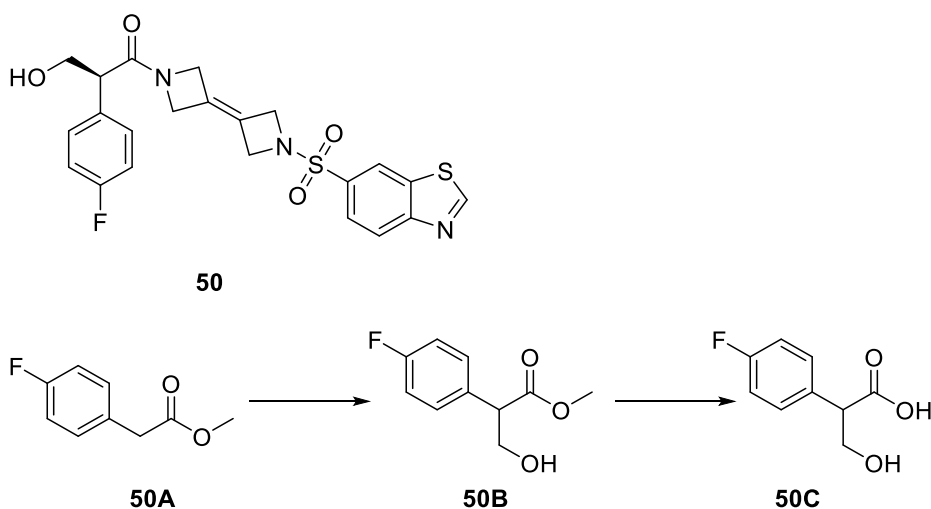


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-6-sulfonyl chloride (the synthesis method was the same as that in Example **20D**), and the same preparation method as that of Example 1 was adopted to obtain **compound 49** of Example 49.

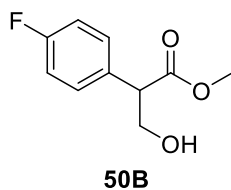
5 MS (ESI) m/z 458.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54-7.50 (t, J = 1.6 Hz, 2H), 7.32-7.21 (m, 5H), 4.50-4.46 (m, 1H), 4.37-4.30 (m, 11H), 3.91-3.86 (t, J = 1.0 Hz, 1H), 3.64-3.61 (m, 2H), 3.48-3.44 (m, 1H).

Example 50: preparation of
 10 (*S*)-1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 50**):



Step 1: preparation of methyl 2-(4-fluorophenyl)-3-hydroxypropionate (**compound 50B**)



15 Methyl 2-(4-fluorophenyl)acetate (2.0 g, 11.89 mmol) was dissolved in dimethyl sulfoxide (20.0 mL), and then added with paraformaldehyde (1.2 g, 12.49 mmol), and then slowly added with sodium methoxide solution (32.1 mg, 594.66 μ mol). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (50.0 mL*3). The organic phases were combined,
 20 washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 50B**.

MS (ESI) m/z 199.0 ($M+H$)⁺.

Step 2: preparation of 2-(4-fluorophenyl)-3-hydroxypropionic acid (**compound 50C**)

Methyl 2-(4-fluorophenyl)-3-hydroxypropionate (1.5 g, 7.47 mmol) was dissolved in a mixed solution
 25 of methanol (15.0 mL) and water (10.0 mL), and then added with sodium hydroxide (597.4 mg, 14.94

mmol). The reaction solution was reacted at 50°C for 3 hours. TLC showed that the reaction was complete. The reaction solution was adjusted to an acidic pH with 1N hydrochloric acid. The aqueous phase was extracted with ethyl acetate (20mL*3). The organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 50C**.

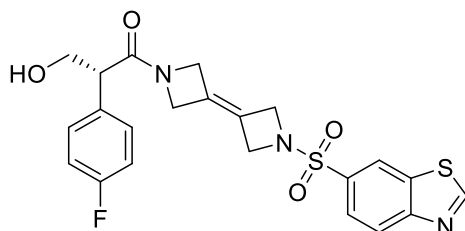
MS (ESI) m/z 185.0 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted, and then the product was subjected to chiral separation to obtain **compound 50** of Example 50.

MS (ESI) m/z 474.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.81-8.80 (d, *J*=4.0 Hz, 1H), 8.34-8.32 (d, *J*=8.0 Hz, 1H), 7.95-7.92 (m, 1H), 7.29-7.25 (m, 2H), 7.11-7.07 (m, 2H), 4.68-4.65 (m, 1H), 4.34-4.25 (m, 7H), 3.82-3.79 (m, 1H), 3.62-3.60 (m, 1H), 3.44-3.40 (m, 2H).

Example 51: preparation of (*R*)-1-(1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-fluorophenyl)-3-hydroxypropan-1-one (**compound 51**):



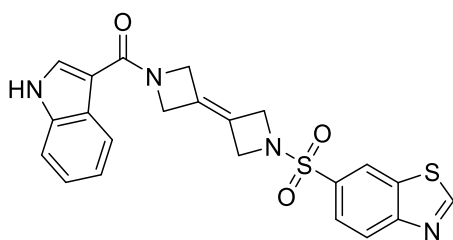
51

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted, and then the product was subjected to chiral separation to obtain **compound 51** of Example 51.

MS (ESI) m/z 474.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.81-8.80 (d, *J*=4.0 Hz, 1H), 8.34-8.32 (d, *J*=8.0 Hz, 1H), 7.95-7.92 (m, 1H), 7.29-7.25 (m, 2H), 7.11-7.07 (m, 2H), 4.68-4.65 (m, 1H), 4.34-4.25 (m, 7H), 3.82-3.79 (m, 1H), 3.62-3.60 (m, 1H), 3.44-3.40 (m, 2H).

Example 52: preparation of (1'-(benzo[*d*]thiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)(1*H*-indol-3-yl)methanone (**compound 52**):



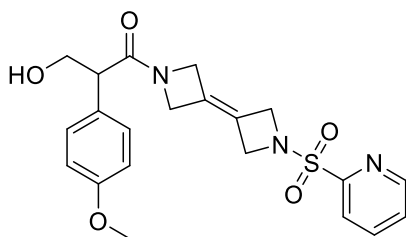
52

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 1*H*-indole-3-carboxylic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 52** of Example 52.

MS (ESI) *m/z* 451.1(*M*+*H*)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.68 (s, 1H), 9.73-9.63 (t, *J* = 4 Hz, 1H), 8.85-8.84 (d, *J* = 0.4 Hz, 1H), 8.36-8.34 (d, *J* = 0.8 Hz, 1H), 8.05-8.03 (d, *J* = 0.8 Hz, 1H), 7.99-7.96 (m, 1H), 7.69-7.68 (d, *J* = 0.4 Hz, 1H), 7.42-7.40 (d, *J* = 0.8 Hz, 1H), 7.16-7.06 (m, 2H), 5.9-4.40 (m, 8H).

Example 53: preparation of 3-hydroxy-2-(4-methoxyphenyl)-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinydene]-1(4*H*)-yl)propan-1-one (**compound 53**):



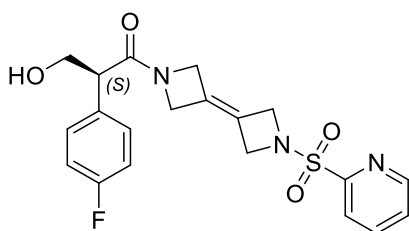
53

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(4-methoxyphenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 53** of Example 53.

MS (ESI) *m/z* 430.1(*M*+*H*)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.79 (m, 1H), 8.17-8.13 (m, 1H), 7.99-7.97 (d, *J* = 8.0 Hz, 1H), 7.76-7.73 (m, 1H), 7.18-7.15 (m, 2H), 6.87-6.83 (m, 2H), 4.76-4.68 (m, 2H), 4.53 (s, 4H), 4.35-4.18 (m, 3H), 3.89-3.81 (m, 1H), 3.71 (s, 3H), 3.57-3.53 (m, 1H), 3.42-3.37 (m, 1H).

Example 54: preparation of (*S*)-2-(4-fluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinydene]-1(4*H*)-yl)propan-1-one (**compound 54**):



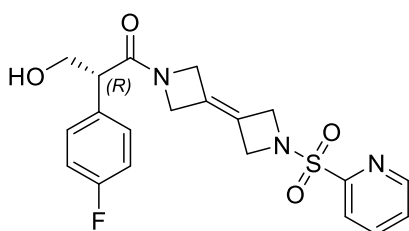
54

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted, and then the product was subjected to chiral separation to obtain **compound 54** of Example 54.

MS (ESI) m/z 418.1($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.80 (d, J = 4.7 Hz, 1H), 8.17-8.13 (m, 1H), 7.99-7.97 (d, J = 7.7 Hz, 1H), 7.77-7.73 (m, 1H), 7.32-7.29 (m, 2H), 7.14-7.09 (m, 2H), 4.83-4.70 (m, 2H), 4.54-4.19 (m, 7H), 3.87-3.82 (m, 1H), 3.66-3.63 (m, 1H), 3.46-3.42 (m, 1H).

Example 55: preparation of (*R*)-2-(4-fluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinyldiene]-1(4*H*)-yl)propan-1-one (**compound 55**):



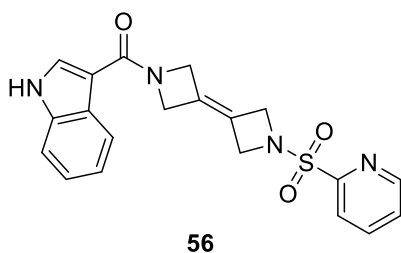
55

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-fluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted, and then the product was subjected to chiral separation to obtain **compound 55** of Example 55.

MS (ESI) m/z 418.1($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.80 (d, J = 4.7 Hz, 1H), 8.17-8.13 (m, 1H), 7.99-7.97 (d, J = 7.7 Hz, 1H), 7.77-7.73 (m, 1H), 7.32-7.29 (m, 2H), 7.14-7.09 (m, 2H), 4.83-4.70 (m, 2H), 4.54-4.19 (m, 7H), 3.87-3.82 (m, 1H), 3.66-3.63 (m, 1H), 3.46-3.42 (m, 1H).

Example 56: preparation of (1*H*-indol-3-yl)(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinyldiene]-1(4*H*)-yl)methanone (**compound 56**):

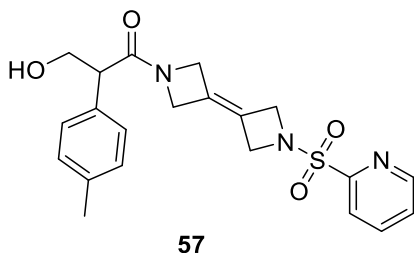


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 1*H*-indole-3-carboxylic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 56** of Example 56.

MS (ESI) m/z 395.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.71 (s, 1H), 8.84 (s, 1H), 8.19-8.16 (t, J = 1.2 Hz, 1H), 8.08-8.06 (d, J = 0.8 Hz, 1H), 8.02-8.00 (d, J = 0.8 Hz, 1H), 7.77-7.73 (d, J = 1.6 Hz, 2H), 7.43-7.41 (d, J = 0.8 Hz, 1H), 7.17-7.08 (m, 2H), 4.60(s, 8H).

Example 57: preparation of 3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(*p*-tolyl)propan-1-one (**compound 57**):

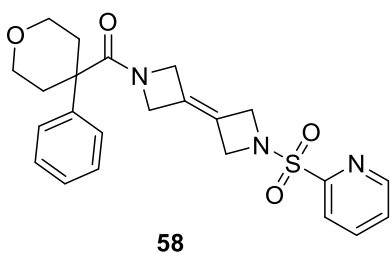


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(*p*-tolyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 57** of Example 57.

MS (ESI) m/z 414.1($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.80-8.79 (m, 1H), 8.17-8.13 (m, 1H), 7.99-7.96 (m, 1H), 7.76-7.73 (m, 1H), 7.14-7.08 (m, 4H), 4.77-4.68 (m, 2H), 4.53 (s, 4H), 4.35-4.18 (m, 3H), 3.89-3.83 (m, 1H), 3.58-3.55 (m, 1H), 3.44-3.39 (m, 1H), 2.25 (s, 3H).

Example 58: preparation of (4-phenyltetrahydro-2*H*-pyran-4-yl)(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)methanone (**compound 58**):

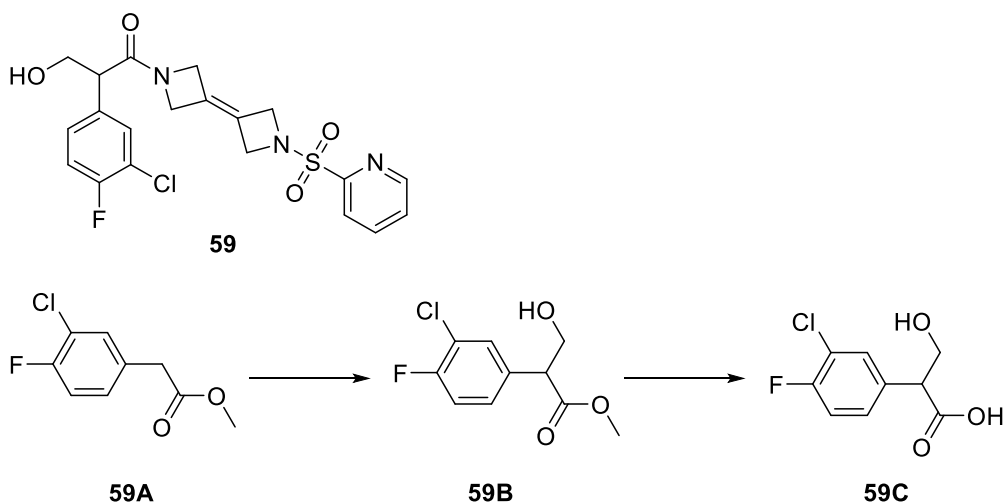


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 4-phenyltetrahydro-2*H*-pyran-4-carboxylic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 58** of Example 58.

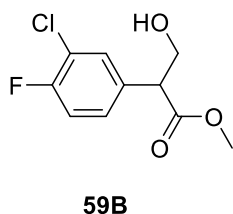
MS (ESI) m/z 440.2($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.78-8.76 (m, 1H), 8.16-8.11 (m, 1H), 7.95-7.93 (d, J = 8.0 Hz, 1H), 7.76-7.73 (m, 1H), 7.40-7.25 (m, 5H), 4.46-3.99 (m, 8H), 3.73-3.70 (m, 2H), 3.56-3.51 (m, 2H), 2.18-2.15 (d, J = 13.5 Hz, 2H), 1.85-1.78 (m, 2H).

Example 59: preparation of 2-(3-chloro-4-fluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 59**):



Step 1: preparation of methyl 2-(3-chloro-4-fluorophenyl)-3-hydroxypropionate (**compound 59B**)

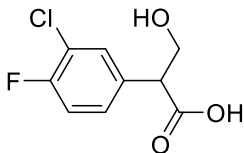


Methyl 2-(3-chloro-4-fluorophenyl)acetate (2.2 g, 10.61 mmol) and paraformaldehyde (477.9 mg, 5.31 mmol) were dissolved in dimethyl sulfoxide (40.0 mL), and then added with sodium methoxide (191.1 mg, 1.06 mmol, 30%). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound**

59B.

MS (ESI) m/z 233.0 (M+H)⁺.

Step 2: preparation of 2-(3-chloro-4-fluorophenyl)-3-hydroxypropionic acid (**compound 59C**)



59C

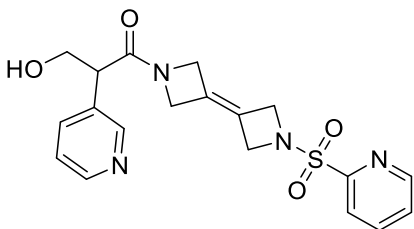
- 5 Methyl 2-(3-chloro-4-fluorophenyl)-3-hydroxypropionate (2.0 g, 8.60 mmol) was dissolved in tetrahydrofuran (60.0 mL) and water (40.0 mL), and then added with sodium hydroxide (687.8 mg, 17.19 mmol), and the reaction solution was stirred at room temperature for 5 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (100 mL*3), and the organic phases were combined, washed with a saturated brine,
10 and dried over anhydrous sodium sulfate. It was concentrated to obtain a yellow oily compound, which was directly used in the next step of reaction.

- In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(3-chloro-4-fluorophenyl)-3-hydroxypropionic acid, and the same preparation
15 method as that of Example 1 was adopted to obtain **compound 59** of Example 59.

MS (ESI) m/z 452.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82-8.81 (m, 1H), 8.19-8.14 (m, 1H), 8.00-7.97 (m, 1H), 7.78-7.74 (m, 1H), 7.51-7.49 (m, 1H), 7.37-7.31 (m, 2H), 4.94-4.87 (m, 1H), 4.78-4.40 (m, 6H), 4.38-4.19 (m, 2H), 3.87-3.77 (m, 2H), 3.55-3.43 (m, 1H).

- 20 **Example 60:** preparation of 3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(pyridin-3-yl)propan-1-one (**compound 60**):



60

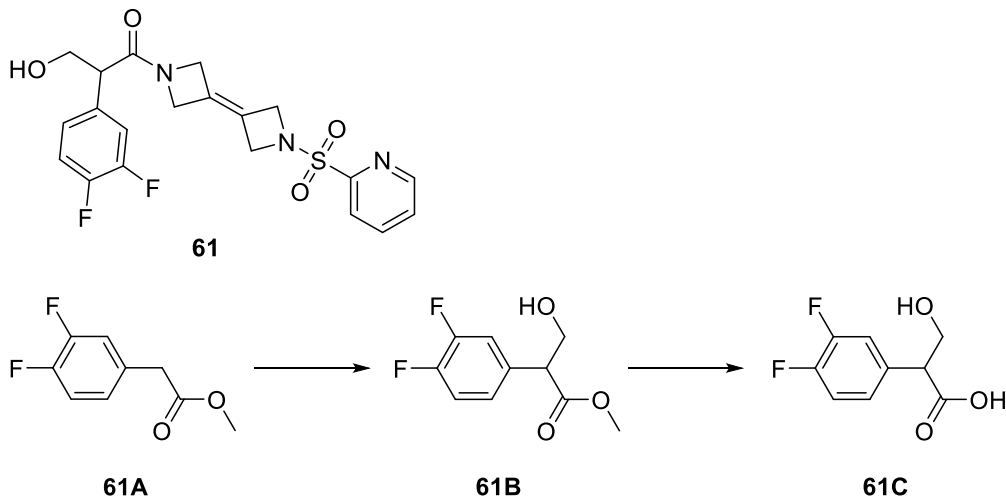
- In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(pyridin-3-yl)propionic acid, and the same preparation method as that of
25 Example 1 was adopted to obtain **compound 60** of Example 60.

MS (ESI) m/z 401.1(M+H)⁺.

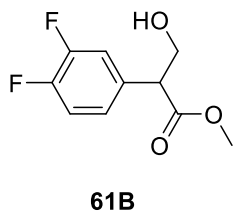
¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.79 (m, 1H), 8.47-8.44 (m, 2H), 8.18-8.13 (m, 1H), 7.99-7.97

(d, $J = 8.0$ Hz, 1H), 7.77-7.69 (m, 2H), 7.34-7.31 (m, 1H), 4.94-4.92 (m, 1H), 4.76-4.73 (d, $J = 12.6$ Hz, 1H), 4.55-4.46 (m, 5H), 4.35-4.21 (m, 2H), 3.91-3.85 (m, 1H), 3.70 (m, 1H), 3.55-3.50 (m, 1H)

Example 61: preparation of 2-(3,4-difluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 61**):



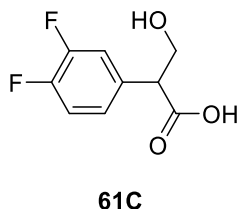
Step 1: preparation of methyl 2-(3,4-difluorophenyl)-3-hydroxypropionate (**compound 61B**)



10 Methyl 2-(3,4-difluorophenyl)acetate (0.5 g, 2.69 mmol) and paraformaldehyde (241.9 mg, 2.69 mmol) were dissolved in dimethyl sulfoxide (10.0 mL), and then added with sodium methoxide (48.4 mg, 0.27 mmol, 30%). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 50C**.

MS (ESI) m/z 217.2 ($M+H$)⁺.

15 **Step 2:** preparation of 2-(3,4-difluorophenyl)-3-hydroxypropionic acid (**compound 61C**)



Methyl 2-(3,4-difluorophenyl)-3-hydroxypropionate (320.0 mg, 1.48 mmol) was dissolved in methanol (15.0 mL) and water (10.0 mL), and then added with sodium hydroxide (118.4 mg, 2.96 mmol). The reaction solution was stirred at 50°C for 3 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (50 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium

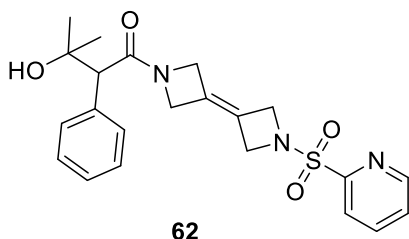
sulfate. After concentration, it was directly used in the next step of reaction.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(3,4-difluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 61** of Example 61.

MS (ESI) *m/z* 436.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82-8.78 (m, 1H), 8.18-8.14 (m, 1H), 8.00-7.95 (m, 1H), 7.79-7.74 (m, 1H), 7.39-7.32 (m, 2H), 7.15-7.11 (m, 1H), 4.90-4.87 (m, 1H), 4.73-4.69 (m, 1H), 4.55-4.44 (m, 5H), 4.34-4.21 (m, 2H), 3.85-3.80 (m, 1H), 3.69-3.65 (m, 1H), 3.50-3.45 (m, 1H).

Example 62: preparation of 3-hydroxy-3-methyl-2-phenyl-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)butan-1-one (**compound 62**):

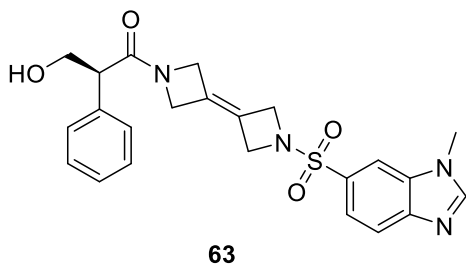


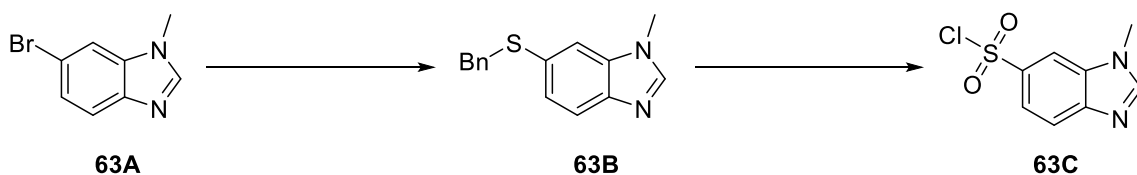
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-3-methyl-2-phenylbutyric acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 62** of Example 62.

MS (ESI) *m/z* 428.2(M+H)⁺.

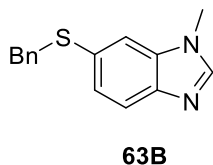
¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79-8.77 (m, 1H), 8.17-8.12 (m, 1H), 7.98-7.96 (d, *J* = 7.7 Hz, 1H), 7.75-7.72 (m, 1H), 7.38-7.22 (m, 5H), 4.89 (brs, 1H), 4.77-4.73 (m, 1H), 4.60-4.45 (m, 4H), 4.35-4.19 (m, 3H), 3.51 (s, 1H), 1.15 (s, 3H), 0.98 (s, 3H).

Example 63: preparation of (*S*)-3-hydroxy-1-(1'-((1-methyl-1*H*-benzimidazol-6-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinyli dene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 63**):





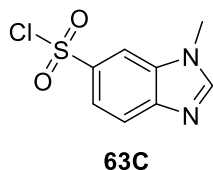
Step 1: preparation of 6-(benzylthio)-1-methyl-1*H*-benzo[*d*]imidazole (**compound 63B**)



6-bromo-1-methyl-1*H*-benzo[*d*]imidazole (1 g, 4.74 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with benzyl mercaptan (588 mg, 4.74 mmol), DIPEA (1.22 g, 9.48 mmol), Pd₂(dba)₃CHCl₃ (485 mg, 0.47 mmol) and xantphos (548 mg, 0.95 mmol). After the addition was completed, the reaction was replaced under nitrogen environment for 3 times, then heated to 80°C, and stirred for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 63B**.

MS (ESI) *m/z* 255.1 (M+H)⁺.

Step 2: preparation of 1-methyl-1*H*-benzo[*d*]imidazole-6-sulfonyl chloride (**compound 63C**)



6-(benzylthio)-1-methyl-1*H*-benzo[*d*]imidazole (560 mg, 2.20 mmol) was dissolved in acetonitrile. Then it was sequentially added with acetic acid (661 mg, 11.01 mmol), water (397 mg, 22.02 mmol) and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (868 mg, 4.40 mmol). After the addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 63C**.

MS (ESI) *m/z* 231.0 (M+H)⁺.

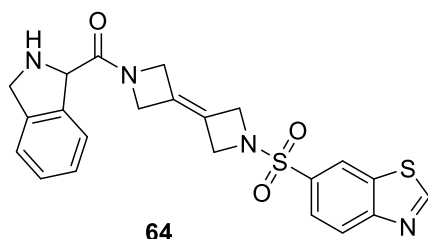
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 1-methyl-1*H*-benzo[*d*]imidazole-6-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 63** of Example 63.

MS (ESI) *m/z* 453.2(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 (s, 1H), 8.17 – 8.04 (m, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.70 – 7.59 (m, 1H), 7.25 (dt, *J* = 13.8, 7.2 Hz, 5H), 4.77 (t, *J* = 5.2 Hz, 1H), 4.67 (d, *J* = 12.5 Hz, 1H), 4.28 (d, *J* = 21.7 Hz, 6H), 4.17 (d, *J* = 14.6 Hz, 1H), 3.96 (s, 3H), 3.86 (td, *J* = 9.4, 5.5 Hz, 1H), 3.59 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.45 (dd, *J* = 9.8, 4.9 Hz, 1H).

Example 64: preparation of (1'-(benzothiazol-6-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)(isoindolin-1-yl)

methanone (**compound 64**):

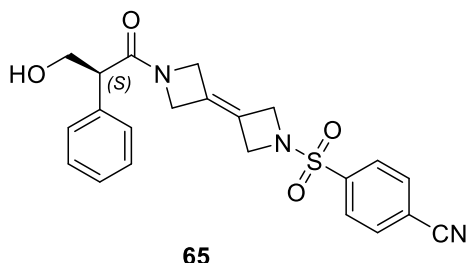


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by benzo[*d*]thiazole-6-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(*tert*-butoxycarbonyl)isoindoline-1-carboxylic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 64** of Example 64.

MS (ESI) m/z 453.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.69 (s, 1H), 8.82 (d, J = 1.8 Hz, 1H), 8.35 (d, J = 8.6 Hz, 1H), 7.96 (dd, J = 8.6, 1.9 Hz, 1H), 7.27 – 7.17 (m, 4H), 4.82 (m, 2H), 4.49 (m, 1H), 4.32 (m, 7H), 4.20 – 4.04 (m, 2H).

Example 65: preparation of (*S*)-4-(1'-(3-hydroxy-2-phenylpropionyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)sulfonyl)benzonitrile (**compound 65**):

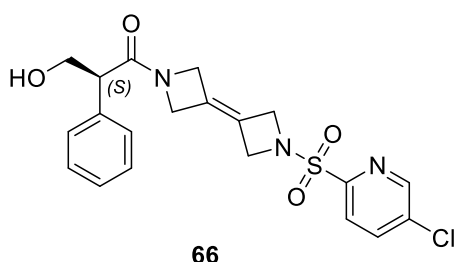


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 4-cyanobenzenesulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 65** of Example 65.

MS (ESI) m/z 424.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19 – 8.13 (m, 2H), 8.03 – 7.98 (m, 2H), 7.32 – 7.18 (m, 5H), 4.79 (t, J = 5.3 Hz, 1H), 4.70 (d, J = 12.5 Hz, 1H), 4.33 (d, J = 15.0 Hz, 6H), 4.19 (d, J = 14.4 Hz, 1H), 3.88 (m, 1H), 3.61 (dd, J = 8.8, 5.5 Hz, 1H), 3.45 (m, 1H).

Example 66: preparation of (*S*)-1-(1'-(5-chloropyridin-2-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 66**):

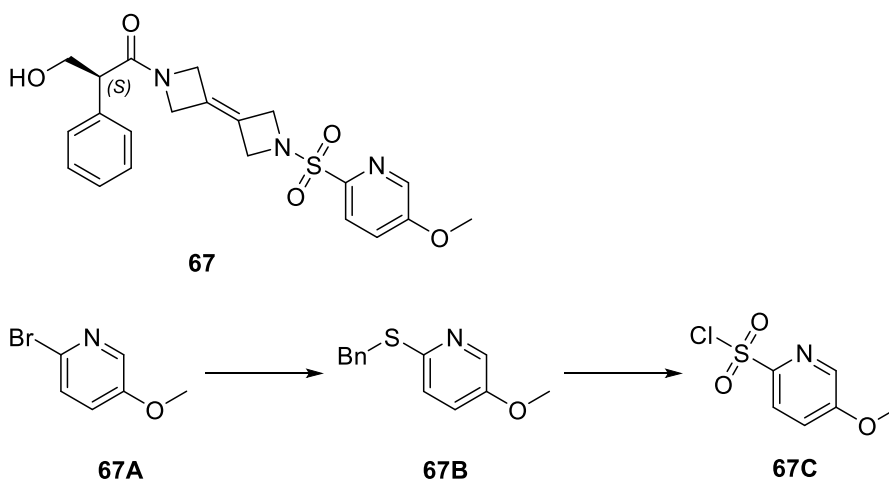


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-chloropyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 66** of Example 66.

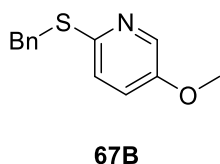
5 MS (ESI) m/z 434.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 – 8.84 (m, 1H), 8.28 (dd, J = 8.4, 2.4 Hz, 1H), 7.99 (dd, J = 8.4, 0.7 Hz, 1H), 7.31 – 7.23 (m, 5H), 4.82 – 4.67 (m, 2H), 4.54 (d, J = 2.8 Hz, 4H), 4.39 – 4.21 (m, 3H), 3.89 (m, 1H), 3.63 (dd, J = 8.9, 5.4 Hz, 1H), 3.46 (m, 1H).

Example 67: preparation of (S)-3-hydroxy-1-(1'-((5-methoxypyridin-2-yl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)-2-phenylpropan-1-one (**compound 67**):



Step 1: preparation of 2-(benzylthio)-5-methoxypyridine (**compound 67B**)



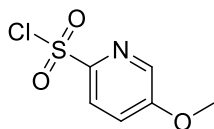
15

2-bromo-5-methoxypyridine (1 g, 5.32 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with benzyl mercaptan (660 mg, 5.32 mmol), DIPEA (1.37 g, 10.64 mmol), Pd₂(dba)₃CHCl₃ (544 mg, 0.53 mmol) and xantphos (615 mg, 1.06 mmol). After the addition was completed, the reaction was replaced under nitrogen environment for 3 times, then heated to 80°C, and stirred for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 67B**.

20

MS (ESI) m/z 232.1(M+H)⁺.

Step 2: preparation of 5-methoxypyridine-2-sulfonyl chloride (**compound 67C**)



67C

2-(benzylthio)-5-methoxypyridine (1.3 g, 5.62 mmol) was dissolved in acetonitrile, and then sequentially added with acetic acid (1.69 g, 28.1 mmol), water (1.01 g, 56.2 mmol) and NCS (1.5 g, 11.24 mmol). After the addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 67C**.

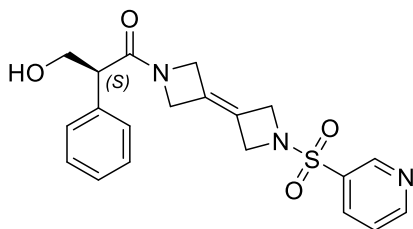
MS (ESI) m/z 208.0 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-methoxypyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 67** of Example 67.

MS (ESI) m/z 430.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 (d, J = 2.9 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.65 (m, 1H), 7.33 – 7.20 (m, 5H), 4.80 (t, J = 5.3 Hz, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.54 – 4.42 (m, 4H), 4.41 – 4.27 (m, 2H), 4.25 – 4.16 (m, 1H), 3.93 (s, 4H), 3.62 (m, 1H), 3.46 (m, 1H).

Example 68: preparation of (S)-3-hydroxy-2-phenyl-1-(1'-(pyridin-3-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propane-1-one (**compound 68**):



68

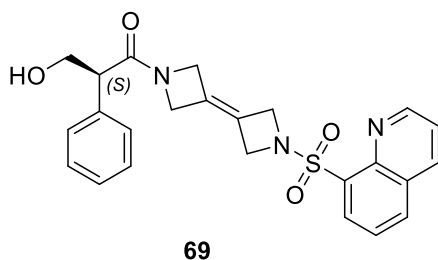
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-3-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 68** of Example 68.

MS (ESI) m/z 400.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (d, J = 2.3 Hz, 1H), 8.92 (dd, J = 4.8, 1.6 Hz, 1H), 8.26 (m, 1H), 7.72 (dd, J = 8.0, 4.9 Hz, 1H), 7.33 – 7.18 (m, 5H), 4.76 – 4.64 (m, 1H), 4.44 – 4.25 (m, 6H), 4.19 (d, J = 13.4 Hz, 1H), 3.88 (t, J = 9.5 Hz, 1H), 3.61 (dd, J = 8.8, 5.5 Hz, 1H), 3.45 (dd, J = 10.1, 5.5 Hz, 2H).

Example 69: preparation of (S)-3-hydroxy-2-phenyl-1-(1'-(quinolin-8-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4

H)-yl)propan-1-one (**compound 69**):

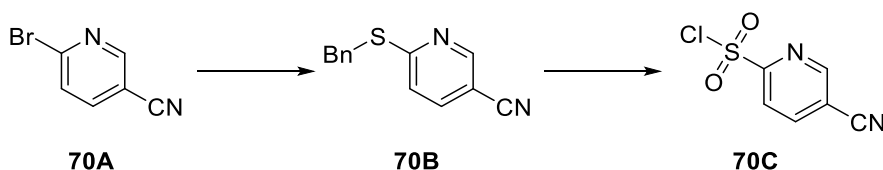
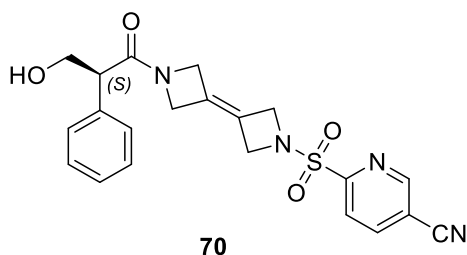


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by quinoline-8-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 69** of Example 69.

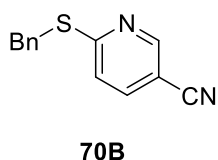
MS (ESI) m/z 450.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (dd, J = 4.2, 1.8 Hz, 1H), 8.56 (dd, J = 8.4, 1.8 Hz, 1H), 8.35 (m, 2H), 7.78 (t, J = 7.8 Hz, 1H), 7.71 (dd, J = 8.3, 4.2 Hz, 1H), 7.33 – 7.19 (m, 5H), 4.92 – 4.59 (m, 6H), 4.40 – 4.28 (m, 2H), 4.22 (m, 1H), 3.89 (t, J = 9.5 Hz, 1H), 3.62 (dd, J = 8.8, 5.5 Hz, 1H), 3.46 (dd, J = 10.1, 5.5 Hz, 1H).

Example 70: preparation of *(S)*-6-((1'-(3-hydroxy-2-phenylpropionyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)sulfonyl)nicotinonitrile (**compound 70**):



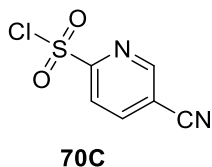
Step 1: preparation of 6-(benzylthio)nicotinonitrile (compound 70B)



2-bromo-5-cyanopyridine (2 g, 14.44 mmol) was dissolved in DMF, and then sequentially added with benzylthiol (1.79 g, 14.44 mmol) and cesium carbonate (5.65 g, 17.33 mmol). After the addition was completed, the reaction was heated to 60°C and stirred for 6 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 70B**.

MS (ESI) m/z 227.1 (M+H)⁺

Step 2: preparation of 5-cyanopyridine-2-sulfonyl chloride (**compound 70C**):



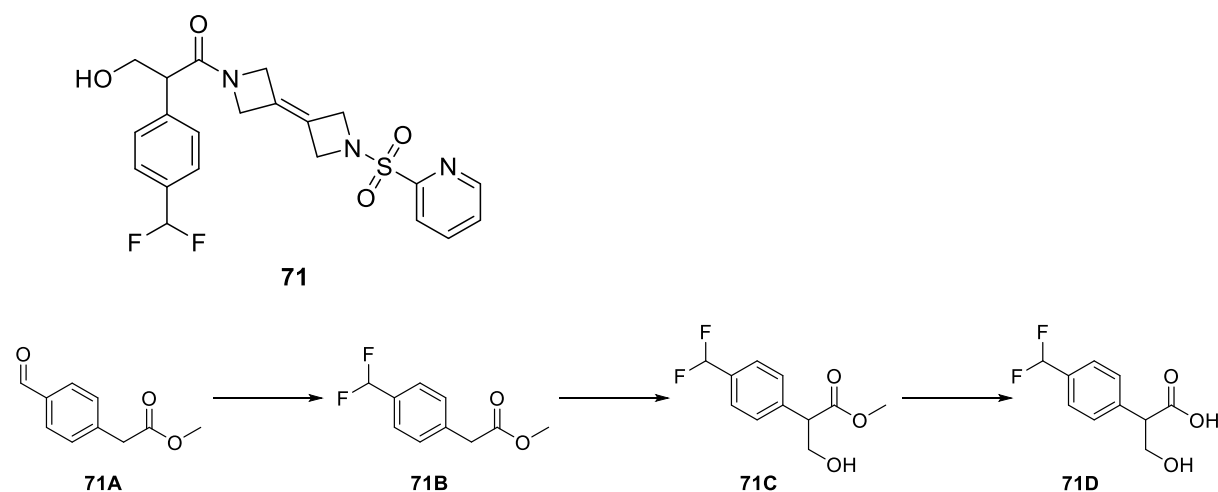
6-(benzylthio)nicotinonitrile (1 g, 4.42 mmol) was dissolved in a mixed solution of dichloromethane and water. The reaction system was cooled to 0°C, and then slowly added dropwise with concentrated hydrochloric acid. After the dropwise addition was completed, the reaction was stirred at 0°C for 10 minutes, and then slowly added dropwise with a sodium hypochlorite aqueous solution. After the dropwise addition was completed, the reaction system was kept at 0°C and stirred for 10 minutes, and then subjected to quick liquid separation. The organic phase was directly used in the next step of reaction.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-cyanopyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 70** of Example 70.

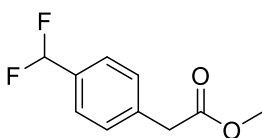
MS (ESI) m/z 425.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.25 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.67 (dd, *J* = 8.2, 2.1 Hz, 1H), 8.14 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.33 – 7.20 (m, 5H), 4.80 (t, *J* = 5.3 Hz, 1H), 4.73 (m, 1H), 4.63 – 4.52 (m, 4H), 4.34 (dd, *J* = 21.7, 8.2 Hz, 2H), 4.27 – 4.18 (m, 1H), 3.90 (m, 1H), 3.63 (dd, *J* = 8.9, 5.5 Hz, 1H), 3.47 (m, 1H).

Example 71: preparation of 2-(4-(difluoromethyl)phenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 71**):



Step 1: preparation of methyl 2-(4-(difluoromethyl)phenyl)acetate (**compound 71B**)

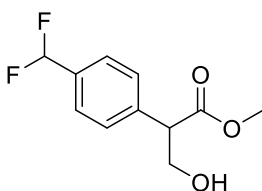


71B

Diethylaminosulfur trifluoride (3.62 g, 22.45 mmol) was added into the solution of methyl 2-(4-formylphenyl)acetate (2.0 g, 11.22 mmol) in dichloromethane (10.0 mL). The mixture was stirred at 50°C under the protection of nitrogen for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 71B**.

MS (ESI) m/z 201.0 (M+H)⁺.

Step 2: preparation of methyl 2-(4-(difluoromethyl)phenyl)-3-hydroxypropionate (**compound 71C**)

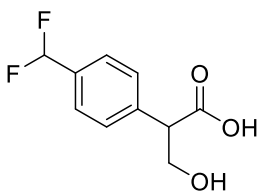


71C

Methyl 2-(4-(difluoromethyl)phenyl)acetate (1.5 g, 7.49 mmol) was dissolved in dimethyl sulfoxide (10.0 mL), then added with paraformaldehyde (681.13 mg, 7.57 mmol), and then slowly added with a sodium methoxide solution (136.23 mg, 756.81 μmol, purity of 30%). The reaction solution was reacted at room temperature for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 71C**.

MS (ESI) m/z 231.0 (M+H)⁺.

Step 3: preparation of 2-(4-(difluoromethyl)phenyl)-3-hydroxypropionic acid (**compound 71D**)



71D

Methyl 2-[4-(difluoromethyl)phenyl]-3-hydroxy-propionate (300 mg, 1.30 mmol) was dissolved in a mixed solution of water (3.0 mL), methanol (3.0 mL) and tetrahydrofuran (3.0 mL), and then added with lithium hydroxide (156.05 mg, 6.52 mmol). The mixture was stirred at 50°C for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 71D**.

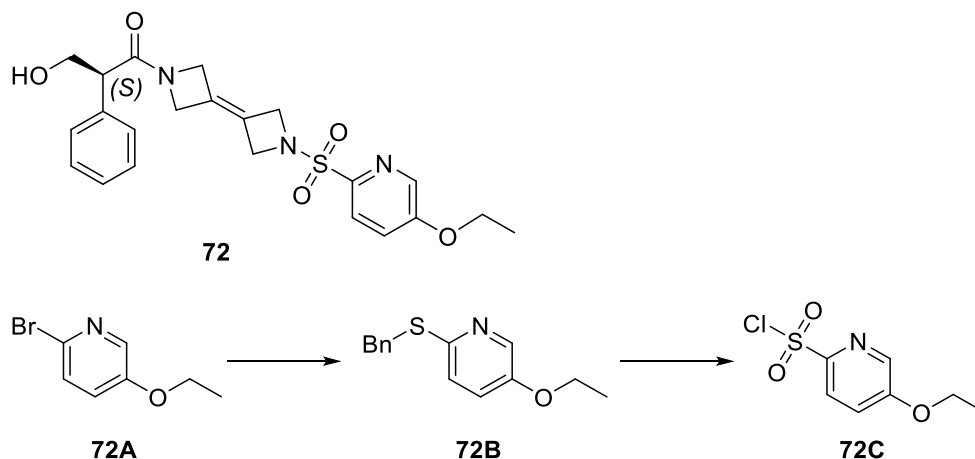
MS (ESI) m/z 217.0 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-(difluoromethyl)phenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 71** of Example 71.

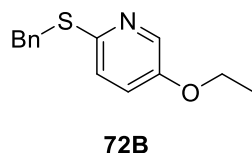
MS (ESI) m/z 450.0 ($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (s, 1H), 8.17-8.13 (t, 1H), 7.98-7.97 (m, 1H), 7.76-7.72 (m, 1H), 7.51-7.49 (d, $J=6.8$ Hz, 2H), 7.42-7.40 (m, $J=6.8$ Hz, 2H), 7.113-6.85 (t, 1 H), 4.87 (s, 1H), 4.75-4.72 (d, $J=12.0$ Hz, 1H), 4.54 (s, 4H), 4.40-4.19 (m, 3 H), 3.88 (s, 1H), 3.71 (s, 1H), 3.49 (s, 1H).

- 5 **Example 72:** preparation of (S)-1-(1'-((5-ethoxypyridin-2-yl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 72**):



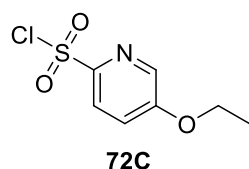
- 10 **Step 1:** preparation of 2-(benzylthio)-5-ethoxypyridine (**compound 72B**)



- 15 2-bromo-5-ethoxypyridine (2 g, 9.9 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with benzyl mercaptan (1.23 g, 9.9mmol), DIPEA (3.28 ml, 19.8 mmol), Pd₂(dba)₃CHCl₃ (1.02 g, 0.99 mmol) and xantphos (1.15 g, 1.98 mmol). After the addition was completed, the reaction was replaced under nitrogen environment for 3 times, then heated to 80°C, and stirred for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 72B**.

MS (ESI) m/z 246.1 ($M+H$)⁺.

Step 2: preparation of 5-ethoxypyridine-2-sulfonyl chloride (**compound 72C**)



20

2-(benzylthio)-5-ethoxypyridine (2.3 g, 9.37 mmol) was dissolved in acetonitrile, into which acetic acid (2.81 g, 46.85 mmol), water (1.69 g, 93.7 mmol) and 1,3-dichloroimidazolidine-2,4-dione (3.69 g, 18.74 mmol) were sequentially added. After the addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a

silica gel column to obtain **compound 72C**.

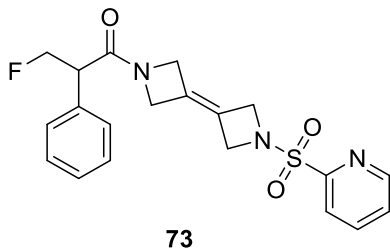
MS (ESI) m/z 221.9 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-ethoxypyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 72** of Example 72.

MS (ESI) m/z 444.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (d, *J* = 2.8 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.63 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.39 – 7.11 (m, 5H), 4.80 (t, *J* = 5.3 Hz, 1H), 4.72 (d, *J* = 13.4 Hz, 1H), 4.47 (s, 4H), 4.40 – 4.26 (m, 2H), 4.22 (q, *J* = 7.0 Hz, 3H), 3.89 (m, 1H), 3.62 (dd, *J* = 8.9, 5.5 Hz, 1H), 3.46 (m, 1H), 1.37 (t, *J* = 6.9 Hz, 3H).

Example 73: preparation of 3-fluoro-2-phenyl-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 73**):

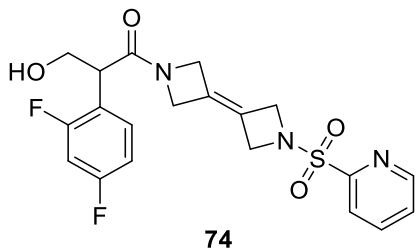


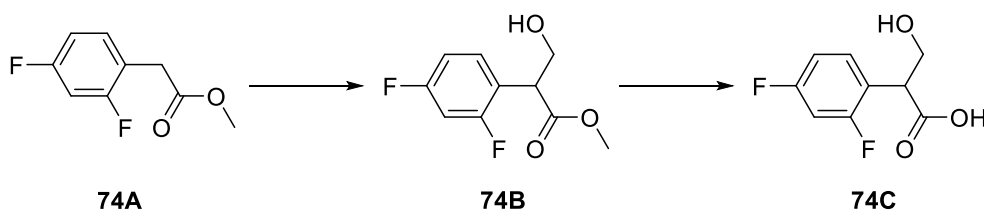
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-fluoro-2-phenylpropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 73** of Example 73.

MS (ESI) m/z 402.1 (M+H)⁺.

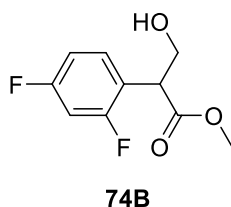
¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.79-8.78 (d, *J* = 8.0 Hz, 1H), 8.17-8.12 (m, 1H), 7.98-7.96 (d, *J* = 8.0 Hz, 1H), 7.76-7.72 (m, 1H), 7.37-7.33 (m, 2H), 7.31-7.23 (m, 3H), 4.89-4.72 (m, 2H), 4.56-4.52 (m, 4H), 4.44-4.21 (m, 4H), 4.06-3.99 (m, 1H).

Example 74: preparation of 2-(2,4-difluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 74**):





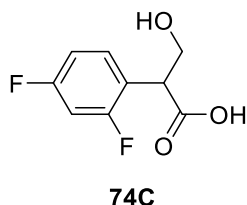
Step 1: preparation of methyl 2-(2,4-difluorophenyl)-3-hydroxypropionate (**compound 74B**)



Methyl 2-(2,4-difluorophenyl)acetate (0.8 g, 4.30 mmol) and paraformaldehyde (387.1 mg, 4.30 mmol) were dissolved in dimethyl sulfoxide (5.0 mL), and then added with sodium methoxide (77.4 mg, 0.43 mmol, 30%). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 74B**.

MS (ESI) m/z 217.2 ($M+H$)⁺.

Step 2: preparation of 2-(2,4-difluorophenyl)-3-hydroxypropionic acid (**compound 74C**)



10

Methyl 2-(2,4-difluorophenyl)-3-hydroxypropionate (440.0 mg, 2.04 mmol) was dissolved in methanol (15.0 mL) and water (10.0 mL), and then added with sodium hydroxide (162.8 mg, 4.07 mmol). The reaction solution was stirred at 50°C for 3 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (50 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. After concentration, it was directly used in the next step of reaction.

15

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(2,4-difluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 74** of Example 74.

20

MS (ESI) m/z 436.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.80 (d, J = 3.8 Hz, 1H), 8.18-8.13 (t, J = 7.7 Hz, 1H), 7.99-7.97 (d, J = 7.7 Hz, 1H), 7.77-7.74 (t, J = 5.9 Hz, 1H), 7.45-7.39 (q, J = 7.7 Hz, 1H), 7.23-7.17 (t, J = 9.8 Hz, 1H), 7.07-7.02 (t, J = 8.4 Hz, 1H), 4.92-4.89 (m, 1H), 4.74-4.71 (m, 1H), 4.60-4.48 (m, 4H), 4.40-4.19 (m, 3H), 3.92-3.82 (m, 2H), 3.55-3.48 (m, 1H).

25

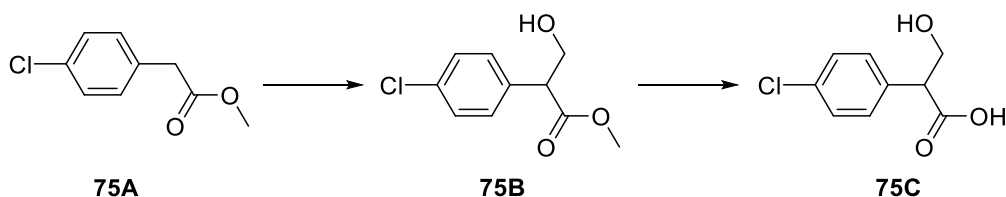
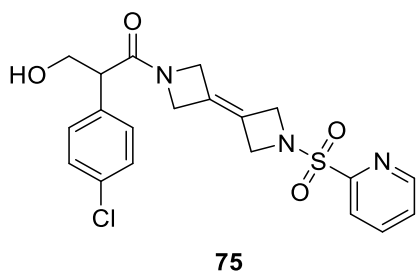
Example

75:

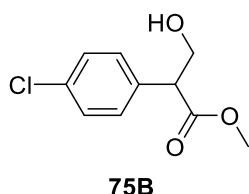
preparation

of

2-(4-chlorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 75**):



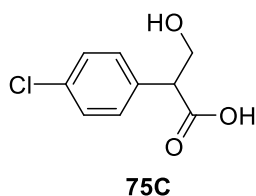
- 5 **Step 1:** preparation of methyl 2-(4-chlorophenyl)-3-hydroxypropionate (**compound 75B**)



Methyl 2-(4-chlorophenyl)acetate (2.0 g, 10.83 mmol) and paraformaldehyde (975.9 mg, 10.83 mmol) were dissolved in dimethyl sulfoxide (50.0 mL), and then added with sodium methoxide (195.1 mg, 1.08 mmol, 30%). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, the reaction solution was diluted with water. The aqueous phase was extracted with ethyl acetate (50 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 75B**.

MS (ESI) m/z 215.1 ($M+H$)⁺

- 15 **Step 2:** preparation of 2-(4-chlorophenyl)-3-hydroxypropionic acid (**compound 75C**)



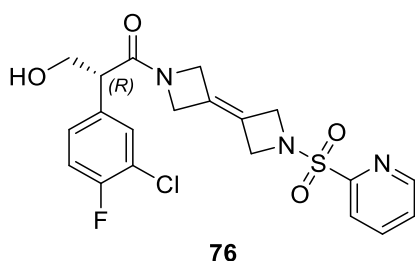
Methyl 2-(4-chlorophenyl)-3-hydroxypropionate (1.3 g, 6.06 mmol) was dissolved in methanol (45.0 mL) and water (30.0 mL), and then added with sodium hydroxide (484.5 mg, 12.11 mmol). The reaction solution was stirred at 50°C for 3 hours. After the reaction was complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with ethyl acetate (50 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. After concentration, it was directly used in the next step of reaction.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-chlorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 75** of Example 75.

5 MS (ESI) *m/z* 434.1(*M*+*H*)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.80 (m, 1H), 8.17-8.12 (m, 1H), 7.99-7.97 (d, *J* = 7.7 Hz, 1H), 7.77-7.73 (m, 1H), 7.38-7.32 (m, 2H), 7.32-7.27 (m, 2H), 4.86-4.83 (t, *J* = 5.2 Hz, 1H), 4.73-4.20 (m, 8H), 3.88-3.82 (m, 1H), 3.67-3.63 (m, 1H), 3.49-3.44 (m, 1H).

10 **Example 76:** preparation of (*R*)-2-(3-chloro-4-fluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(*4H*)-yl)propan-1-one (**compound 76**):

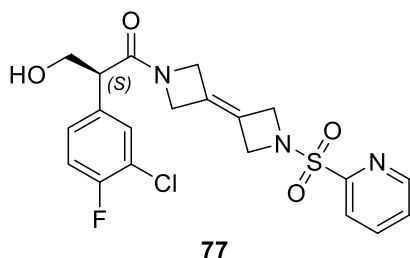


15 In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(3-chloro-4-fluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted, and then the product was subjected to chiral separation to obtain **compound 76** of Example 76.

MS (ESI) *m/z* 452.1(*M*+*H*)⁺.

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82-8.81 (m, 1H), 8.19-8.14 (m, 1H), 8.00-7.97 (m, 1H), 7.78-7.74 (m, 1H), 7.51-7.49 (m, 1H), 7.37-7.31 (m, 2H), 4.94-4.87 (m, 1H), 4.78-4.40 (m, 6H), 4.38-4.19 (m, 2H), 3.87-3.77 (m, 2H), 3.55-3.43 (m, 1H).

Example 77: preparation of (*S*)-2-(3-chloro-4-fluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(*4H*)-yl)propan-1-one (**compound 77**):



25

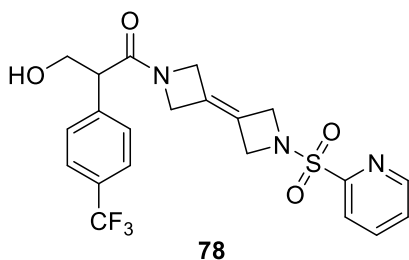
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(3-chloro-4-fluorophenyl)-3-hydroxypropionic acid, the same preparation method as

that of Example 1 was adopted, and then the product was subjected to chiral separation to obtain **compound 77** of Example 77.

MS (ESI) m/z 452.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82-8.81 (m, 1H), 8.19-8.14 (m, 1H), 8.00-7.97 (m, 1H), 7.78-7.74 (m, 1H), 7.51-7.49 (m, 1H), 7.37-7.31 (m, 2H), 4.94-4.87 (m, 1H), 4.78-4.40 (m, 6H), 4.38-4.19 (m, 2H), 3.87-3.77 (m, 2H), 3.55-3.43 (m, 1H).

Example 78: preparation of 3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-(4-(trifluoromethyl)phenyl)propan-1-one (**compound 78**):

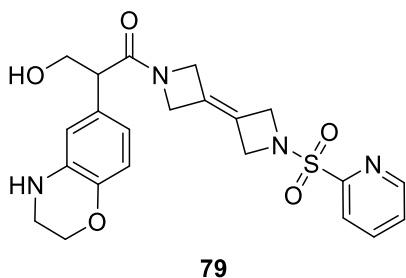


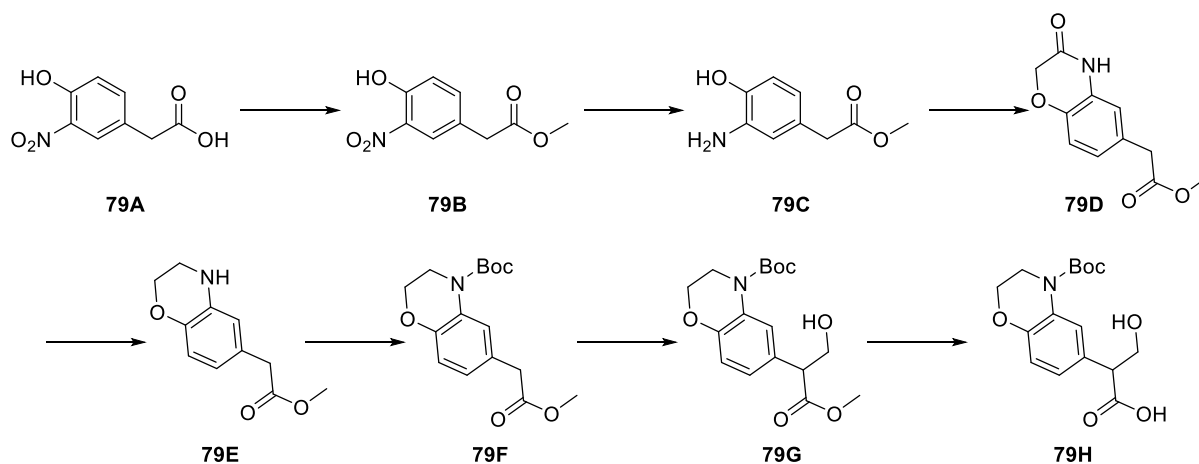
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-hydroxy-2-(4-(trifluoromethyl)phenyl)propionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 78** of Example 78.

MS (ESI) m/z 468.1(M+H)⁺.

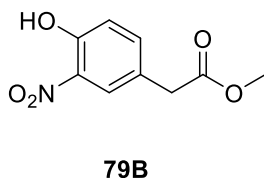
¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.79 (d, *J* = 4.7 Hz, 1H), 8.18-8.13 (m, 1H), 7.99-7.97 (d, *J* = 8.0 Hz, 1H), 7.76-7.73 (m, 1H), 7.67-7.65 (d, *J* = 8.2 Hz, 2H), 7.52-7.50 (d, *J* = 8.2 Hz, 2H), 4.76-4.73 (d, *J* = 12.4 Hz, 1H), 4.54 (s, 4H), 4.43-4.39 (d, *J* = 13.2 Hz, 1H), 4.34-4.31 (d, *J* = 13.7 Hz, 1H), 4.24-4.21 (d, *J* = 12.9 Hz, 1H), 3.91-3.87 (m, 1H), 3.78-3.75 (m, 1H), 3.54-3.50 (m, 1H), 2.67-2.65 (d, *J* = 7.4 Hz, 1H).

Example 79: preparation of 2-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 79**):





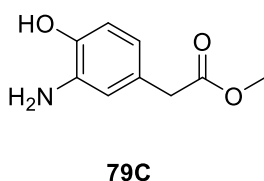
Step 1: preparation of methyl 2-(4-hydroxy-3-nitrophenyl)acetate (**compound 79B**)



2-(4-hydroxy-3-nitrophenyl)acetic acid (5.0 g, 25.36 mmol) was dissolved in anhydrous methanol (100 mL), and then slowly added with thionyl chloride (6.03 g, 50.72 mmol). The reaction solution was reacted at room temperature for 3 hours. After the reaction was complete, the reaction solution was diluted with water. The aqueous phase was extracted with ethyl acetate (100 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 79B**.

MS (ESI) m/z 212.1 ($M+H$)⁺

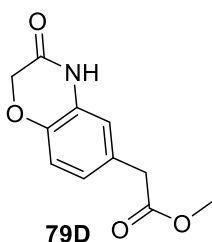
Step 2: preparation of methyl 2-(3-amino-4-hydroxyphenyl)acetate (**compound 79C**)



Methyl 2-(4-hydroxy-3-nitrophenyl)acetate (4.7 g, 22.3 mmol) was dissolved in absolute ethanol (100.0 mL), and then added with palladium on carbon (470 mg, 2.23 mmol). The reaction solution was stirred at room temperature for 16 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (100 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 79C**.

MS (ESI) m/z 182.1 ($M+H$)⁺.

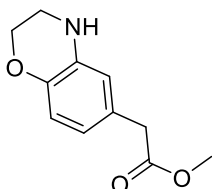
Step 3: preparation of methyl 2-(3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)acetate (**compound 79D**)



Methyl 2-(4-fluoro-2-methoxyphenyl)acrylate (3.5 g, 19.3 mmol) was dissolved in ethyl acetate (100 mL) and water (100 mL), and then added with sodium carbonate (4.19 g, 38.6 mmol) and 2-chloroacetyl chloride (2.16 g, 19.3 mmol). The reaction solution was stirred at room temperature for 4 hours. After the reaction was complete, the product was extracted with ethyl acetate (200 mL) for 3 times, and the organic phases were combined, and separated and purified through a silica gel column to obtain **compound 79D**.

MS (ESI) m/z 222.1 ($M+H$)⁺.

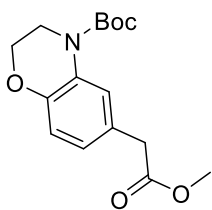
Step 4: preparation of methyl 2-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acetate (**compound 79E**)



Methyl 2-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acetate (2.4 g, 10.9 mmol) was dissolved in tetrahydrofuran (100.0 mL), and then added with the solution of borane in tetrahydrofuran (1.87 g, 21.7 mmol). The reaction solution was stirred at 60°C for 12 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (100 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 79E**.

MS (ESI) m/z 208.1 ($M+H$)⁺.

Step 5: preparation of tert-butyl 6-(2-methoxy-2-oxoethyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (**compound 79F**)

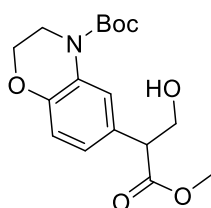


Methyl 2-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acetate (1.2 g, 5.45 mmol) was dissolved in dichloromethane (100 mL), and then added with triethylamine (1.18 g, 10.9 mmol) and 4-dimethylaminopyridine (662.7 mg, 5.45 mmol). The reaction system was cooled to 0°C, and then slowly added with di-tert-butyl dicarbonate (1.77 g, 8.14 mmol), and the reaction solution was stirred at

room temperature for 16 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (100 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 79F**.

5 MS (ESI) m/z 308.1 (M+H)⁺.

Step 6: preparation of tert-butyl 6-(3-hydroxy-1-methoxy-1-oxopropan-2-yl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (**compound 79G**)

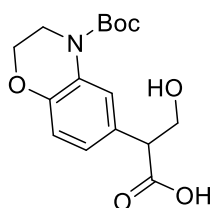


79G

10 Tert-butyl 6-(2-methoxy-2-oxoethyl)-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (576 mg, 1.87 mmol) and paraformaldehyde (168.9 mg, 1.87mmol) were dissolved in dimethyl sulfoxide (50.0 mL), and then added with sodium methoxide (10.1 mg, 0.19 mmol). The reaction solution was reacted at room temperature for 4 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (10 mL*3). The organic phases were
15 combined, washed with a saturated brine, and dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 79F**.

MS (ESI) m/z 338.4 (M+H)⁺.

Step 7: preparation of 2-(4-(tert-butoxycarbonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-3-hydroxypropionic acid (**compound 79H**)



79H

Methyl 3-hydroxy-2-(naphthalene-2-yl)propionate (235.0 mg, 0.69 mmol) was dissolved in anhydrous methanol (60.0 mL) and water (40.0 mL), and then added with sodium hydroxide (27.8 mg, 0.69 mmol). The reaction solution was stirred at room temperature for 5 hours. After the reaction was
25 complete, the reaction solution was adjusted to pH 2 with 1N hydrochloric acid, and extracted with dichloromethane (100 mL*3), and the organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. It was concentrated to obtain a yellow oily compound, which was directly used in the next step of reaction.

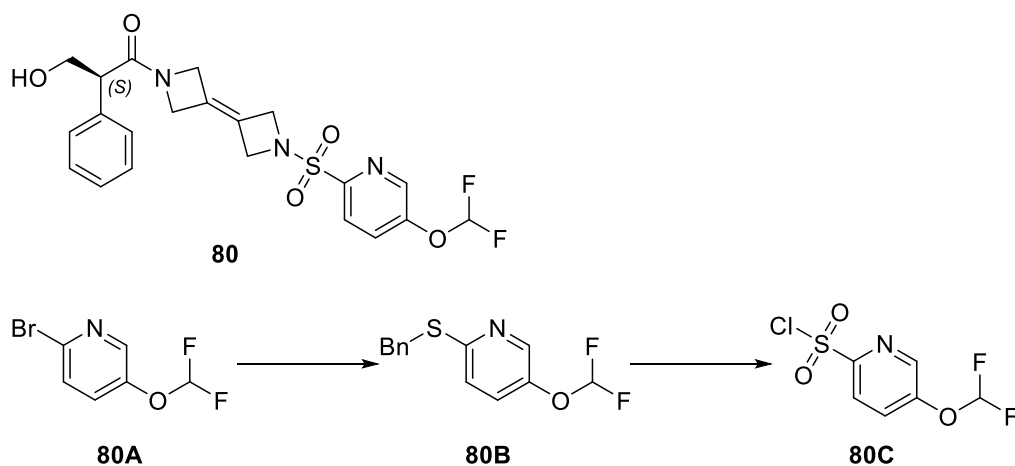
In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by

pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted to obtain **compound 79** of Example 79.

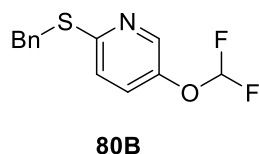
5 MS (ESI) m/z 457.2($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.82-8.81 (m, 1H), 8.17-8.14(m, 1H), 8.00-7.98 (d, *J* = 8.0 Hz, 1H), 7.78-7.74 (m, 1H), 6.55-6.31 (m, 3H), 5.75 (s, 1H), 4.70-4.67 (m, 2H), 4.55 (s, 4H), 4.33-4.20 (m, 3H), 4.08-4.06 (m, 2H), 3.87-3.80 (m, 1H), 3.41-3.38 (m, 2H), 3.24 (s, 2H).

10 **Example 80:** preparation of (*S*)-1-(1'-((5-(difluoromethoxy)pyridin-2-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 80**):



Step 1: preparation of 2-(benzylthio)-5-(difluoromethoxy)pyridine (**compound 80B**)



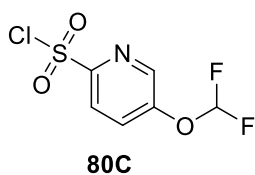
15

2-bromo-5-difluoromethoxypyridine (2 g, 8.93 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with benzyl mercaptan (1.11 g, 8.93 mmol), DIPEA (2.31 g, 17.86 mmol), Pd₂(dba)₃CHCl₃ (913 mg, 0.89 mmol) and xantphos (1.03 g, 1.79 mmol). After the addition was completed, the reaction was replaced under nitrogen environment for 3 times, then heated to 80°C, and stirred for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 80B**.

20

MS (ESI) m/z 268.1 ($M+H$)⁺.

Step 2: preparation of 5-(difluoromethoxy)pyridine-2-sulfonyl chloride (**compound 80C**)



2-(benzylthio)-5-difluoromethoxypyridine (1.0 g, 3.74 mmol) was dissolved in acetonitrile, into which acetic acid (1.12 g, 18.71 mmol), water (674 mg, 37.41 mmol) and 1,3-dichloro-5,5-dimethylhydantoin (1.47 g, 7.48 mmol) were sequentially added. After the addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 80C**.

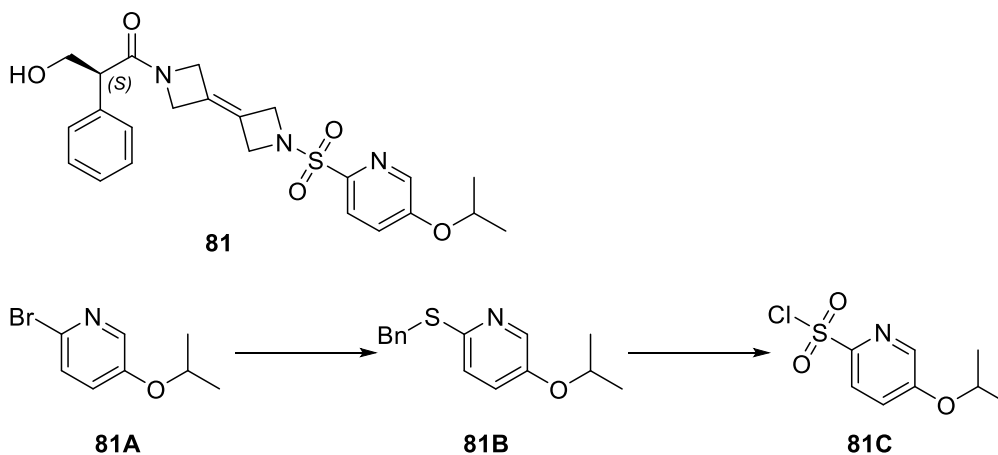
MS (ESI) m/z 244.0 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-(difluoromethoxy)pyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 80** of Example 80.

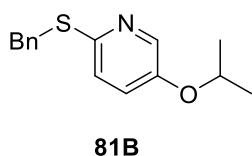
MS (ESI) m/z 466.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (d, J = 2.7 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.95 (dd, J = 8.7, 2.7 Hz, 1H), 7.50 (s, 1H), 7.34 – 7.19 (m, 5H), 4.80 (t, J = 5.3 Hz, 1H), 4.73 (d, J = 13.3 Hz, 1H), 4.53 (s, 4H), 4.42 – 4.27 (m, 2H), 4.22 (d, J = 15.0 Hz, 1H), 3.89 (m, 1H), 3.63 (dd, J = 8.8, 5.5 Hz, 1H), 3.46 (m, 1H).

Example 81: preparation of (S)-3-hydroxy-1-(1'-((5-isopropoxypyridin-2-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 81**):



Step 1: preparation of 2-(benzylthio)-5-isopropoxypyridine (**compound 81B**)

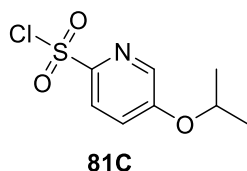


2-bromo-5-isopropoxypyridine (2 g, 9.26 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with benzyl mercaptan (1.15 g, 9.26 mmol), DIPEA (2.39 g, 18.51 mmol),

$\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ (947 mg, 0.93 mmol) and xantphos (1.07 g, 1.85 mmol). After the addition was completed, the reaction was replaced under nitrogen environment for 3 times, then heated to 80°C, and stirred for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 81B**.

5 MS (ESI) m/z 260.1($\text{M}+\text{H}$)⁺.

Step 2: preparation of 5-isopropoxy-pyridine-2-sulfonyl chloride (**compound 81C**)



2-(benzylthio)-5-isopropoxy-pyridine (1.0 g, 3.86 mmol) was dissolved in acetonitrile, into which acetic acid (1.16 g, 19.28 mmol), water (695 mg, 38.56 mmol) and 1,3-dichloro-5,5-dimethylhydantoin (1.52 g, 7.71 mmol) were sequentially added. After the material addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 81C**.

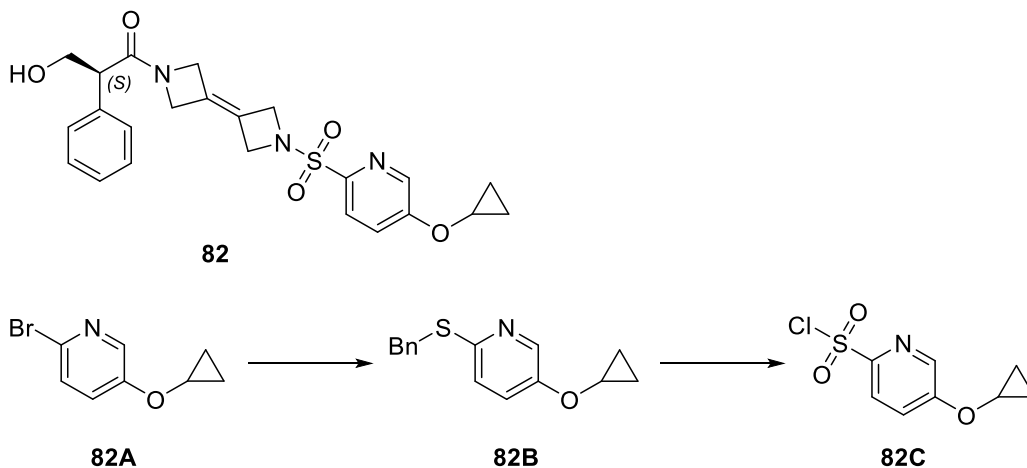
MS (ESI) m/z 236.0($\text{M}+\text{H}$)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-isopropoxy-pyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted to obtain **compound 81** of Example 81.

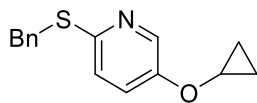
MS (ESI) m/z 458.2($\text{M}+\text{H}$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (d, J = 2.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 8.8, 2.8 Hz, 1H), 7.26 (m, 5H), 4.82 (m, 2H), 4.72 (d, J = 13.3 Hz, 1H), 4.47 (s, 4H), 4.42 – 4.26 (m, 2H), 4.21 (d, J = 14.6 Hz, 1H), 3.89 (m, 1H), 3.62 (dd, J = 8.9, 5.5 Hz, 1H), 3.46 (m, 1H), 1.32 (d, J = 6.0 Hz, 6H).

Example 82: preparation of (S)-1-(1'-((5-cyclopropoxy-pyridin-2-yl)sulfonyl)-1',4'-dihydro-2H,2'H-[3,3'-diazetidinylidene]-1(4H)-yl)-3-hydroxy-2-phenylpropan-1-one (**compound 82**):



Step 1: preparation of 2-(benzylthio)-5-cyclopropoxypyridine (compound 82B)

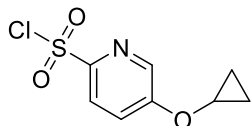


82B

2-bromo-5-cyclopropoxypyridine (3.98 g, 18.59 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with benzyl mercaptan (2.31 g, 18.59mmol), DIPEA (7.21 g, 55.77mmol),
5 Pd₂(dba)₃CHCl₃ (1.92 g, 1.86 mmol) and xantphos (2.15 g, 3.72 mmol). After the addition was completed, the reaction was replaced under nitrogen environment for 3 times, then heated to 80°C, and stirred for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 82B**.

MS (ESI) m/z 258.1 (M+H)⁺.

10 **Step 2: preparation of 5-cyclopropoxypyridine-2-sulfonyl chloride (compound 82C)**



82C

2-(benzylthio)-5-cyclopropoxypyridine (2.0 g, 7.78 mmol) was dissolved in acetonitrile, into which acetic acid (2.33 g, 38.9 mmol), water (1.40 g, 77.8 mmol) and 1,3-dichloroimidazolidine-2,4-dione (3.06 g, 15.56 mmol) were sequentially added. After the addition was completed, the reaction was
15 stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 82C**.

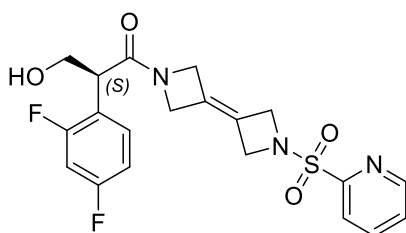
MS (ESI) m/z 233.9 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-cyclopropoxypyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1
20 was adopted to obtain **compound 82** of Example 82.

MS (ESI) m/z 456.2(M+H)⁺.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 2.8 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.53 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.25 – 7.19 (m, 2H), 4.50 (d, *J* = 29.8 Hz, 7H), 4.19 – 3.92 (m, 2H), 3.86 (m, *J* = 6.4, 2.9 Hz, 1H), 3.71 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.65 (dd, *J* = 8.8, 4.4 Hz, 1H), 0.97
25 – 0.79 (m, 4H).

Example 83: preparation of
(*S*)-2-(2,4-difluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 83**):



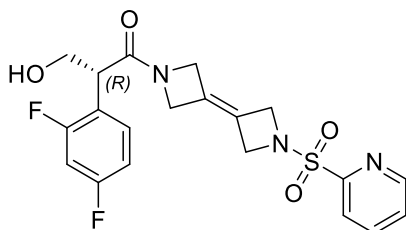
83

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(2,4-difluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted for separation, and then the product was subjected to chiral separation to obtain **compound 83** of Example 83.

MS (ESI) m/z 436.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.80 (d, J = 3.8 Hz, 1H), 8.18-8.13 (t, J = 7.7 Hz, 1H), 7.99-7.97 (d, J = 7.7 Hz, 1H), 7.77-7.74 (t, J = 5.9 Hz, 1H), 7.45-7.39 (q, J = 7.7 Hz, 1H), 7.23-7.17 (t, J = 9.8 Hz, 1H), 7.07-7.02 (t, J = 8.4 Hz, 1H), 4.92-4.89 (m, 1H), 4.74-4.71 (m, 1H), 4.60-4.48 (m, 4H), 4.40-4.19 (m, 3H), 3.92-3.82 (m, 2H), 3.55-3.48 (m, 1H).

Example 84: preparation of (*R*)-2-(2,4-difluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 84**):



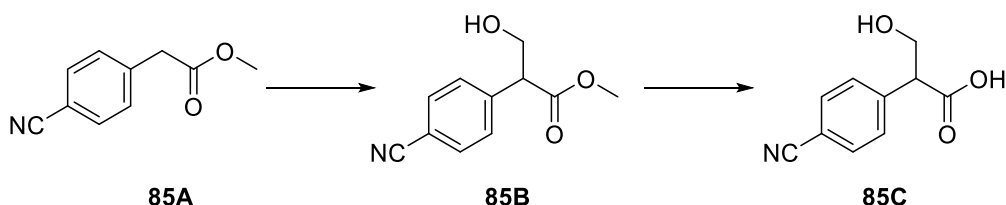
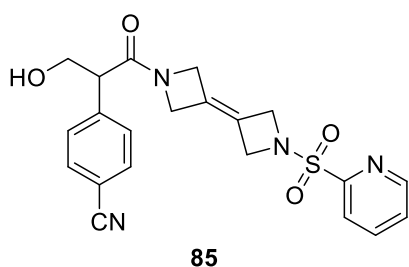
84

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(2,4-difluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted for separation, and then the product was subjected to chiral separation to obtain **compound 84** of Example 84.

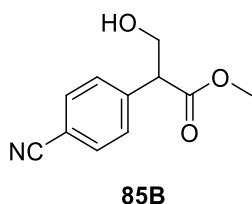
MS (ESI) m/z 436.1($M+H$)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81-8.80 (d, J = 3.8 Hz, 1H), 8.18-8.13 (t, J = 7.7 Hz, 1H), 7.99-7.97 (d, J = 7.7 Hz, 1H), 7.77-7.74 (t, J = 5.9 Hz, 1H), 7.45-7.39 (q, J = 7.7 Hz, 1H), 7.23-7.17 (t, J = 9.8 Hz, 1H), 7.07-7.02 (t, J = 8.4 Hz, 1H), 4.92-4.89 (m, 1H), 4.74-4.71 (m, 1H), 4.60-4.48 (m, 4H), 4.40-4.19 (m, 3H), 3.92-3.82 (m, 2H), 3.55-3.48 (m, 1H)

Example 85: preparation of 4-(3-hydroxy-1-oxo-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-2-yl)benzonitrile (**compound 85**):



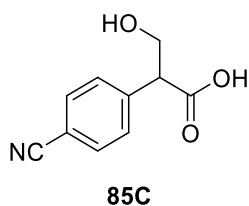
Step 1: preparation of methyl 2-(4-cyanophenyl)-3-hydroxypropionate (**compound 85B**)



5 Methyl 2-(4-cyanophenyl)acetate (1.0 g, 5.71 mmol), paraformaldehyde (257 mg, 2.85 mmol) and sodium bicarbonate (14 mg, 0.17 mmol) were dissolved in a dimethyl sulfoxide solution (10 mL). After the addition was completed, the reaction system was placed and stirred at room temperature for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 85B**.

10 MS (ESI) m/z 206.1 ($M+H$)⁺.

Step 2: preparation of 2-(4-cyanophenyl)-3-hydroxypropionic acid (**compound 85C**)



15 Methyl 3-hydroxy-2-(4-cyanophenyl)propionate (0.2 g, 0.97 mmol) and lithium hydroxide monohydrate (82 mg, 1.95 mmol) were dissolved in a mixed solution of methanol (3.0 mL) and water (1 mL). After the addition was completed, the reaction system was placed and stirred at room temperature overnight. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 85C**.

MS (ESI) m/z 192.2 ($M+H$)⁺.

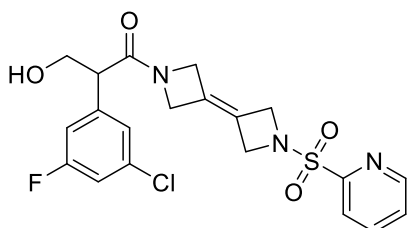
20 In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(4-cyanophenyl)-3-hydroxypropionic acid, and the same preparation method as that

of Example 1 was adopted for separation to obtain **compound 85** of Example 85.

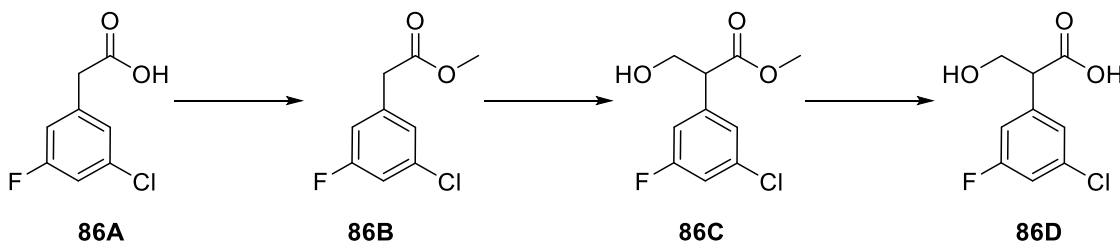
MS (ESI) m/z 425.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82-8.81 (m, 1H), 8.17-8.14 (t, *J* = 1.2 Hz, 1H), 8.00-7.98 (d, *J* = 0.8Hz, 1H), 7.79-7.77 (m, 3H), 7.51-7.48 (d, *J* = 1.2 Hz, 2H), 4.94-4.92 (d, *J* = 0.8 Hz, 1H), 4.75-4.72 (d, *J* = 1.2 Hz, 1H), 4.55-4.25 (m, 6H), 3.91-3.81 (m, 1H), 3.79-3.77 (t, *J* = 0.8 Hz, 1H), 3.56-3.38 (m, 2H).

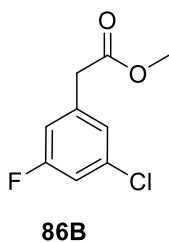
Example 86: preparation of 2-(3-chloro-5-fluorophenyl)-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 86**):



10



Step 1: preparation of methyl 2-(3-chloro-5-fluorophenyl)acetate (**compound 86B**)

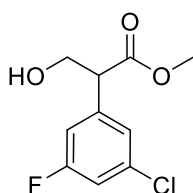


15

2-(3-chloro-5-fluorophenyl)acetic acid (1 g, 5.30 mmol) was dissolved in methanol (10 mL), and then added with thionyl chloride (1.25 g, 10.59 mmol) at 0°C. After the addition was completed, the reaction system was placed and stirred at 60°C under nitrogen atmosphere for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 86B**.

MS (ESI) m/z 201.2 (M-H)⁻.

Step 2: preparation of methyl 2-(3-chloro-5-fluorophenyl)-3-hydroxypropionate (**compound 86C**)

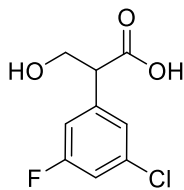


86C

Methyl 2-(3-chloro-5-fluorophenyl)acetate (1.01 g, 4.98 mmol) was dissolved in dimethyl sulfoxide (10 mL), and then added with sodium methoxide (90 mg, 500.00 μ mol) and paraformaldehyde (220 mg, 2.44 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at room temperature under nitrogen atmosphere for 1 hour. The reaction solution was diluted by adding water, the aqueous phase was extracted with ethyl acetate (10.0 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 86C**.

MS (ESI) m/z 233.1 ($M+H$)⁺.

Step 3: preparation of 2-(3-chloro-5-fluorophenyl)-3-hydroxypropionic acid (**compound 86D**)



86D

Methyl 2-(3-chloro-5-fluorophenyl)-3-hydroxypropionate (200 mg, 859.71 μ mol) was dissolved in tetrahydrofuran (3 mL) and water (3 mL), and added with lithium hydroxide (72 mg, 1.71 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at room temperature under nitrogen atmosphere for 2 hours. After the reaction was completed, the reaction solution was concentrated and adjusted to the pH value of 3-4 with 1N hydrochloric acid solution. The aqueous phase was extracted with ethyl acetate (10.0 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 86D**.

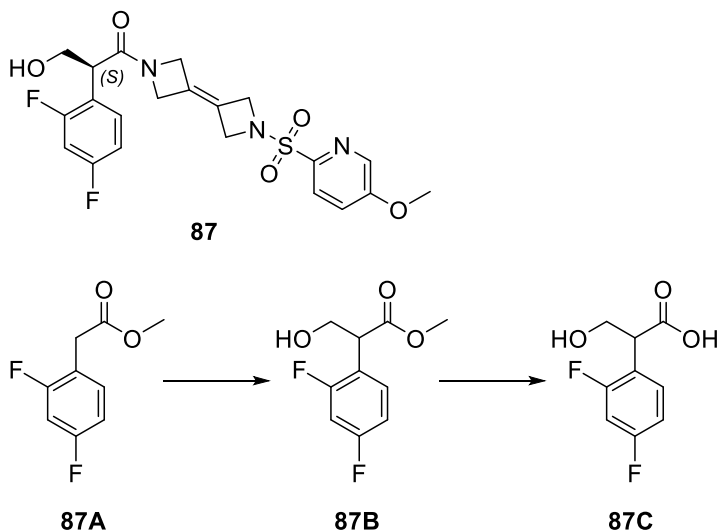
MS (ESI) m/z 217.1 ($M-H$)⁻.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(3-chloro-5-fluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted for separation to obtain **compound 86** of Example 86.

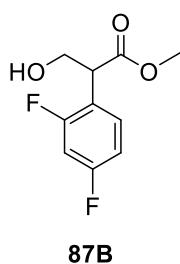
MS (ESI) m/z 452.1($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.82-8.81 (m, 1H), 8.16-8.14 (m, 1H), 8.00-7.98 (m, 1H), 7.77-7.74 (m, 1H), 7.34-7.30 (m, 1H), 7.24 (s, 1H), 7.17-7.14 (m, 1H), 4.94 (t, *J* = 5.2 Hz, 1H), 4.74-4.70 (m, 1H), 4.55-4.50 (m, 5H), 4.35-4.23 (m, 2H), 3.86- 3.80 (m, 1H), 3.73-3.70 (m, 1H), 3.54-3.49 (m, 1H).

Example 87: preparation of *(S)*-2-(2,4-difluorophenyl)-3-hydroxy-1-(1'-((5-methoxypyridin-2-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 87**):



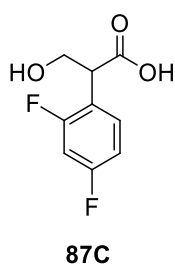
Step 1: preparation of methyl 2-(2,4-difluorophenyl)-3-hydroxypropionate (**compound 87B**)



Methyl 2-(2,4-difluorophenyl)acetate (820 mg, 4.40 mmol) was dissolved in dimethyl sulfoxide (8 mL), and then added with sodium methoxide (80 mg, 444.44 μmol , purity of 30%) and paraformaldehyde (200 mg, 2.22 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at room temperature under nitrogen atmosphere for 3 hours. After the reaction was complete, the reaction solution was diluted by adding water. The aqueous phase was extracted with ethyl acetate (30.0 mL*3), and the organic phases were combined, washed with a saturated brine, and then dried over anhydrous sodium sulfate, and separated and purified through a silica gel column to obtain **compound 87B**.

MS (ESI) m/z 217.1 ($M+H$)⁺.

Step 2: preparation of 2-(2,4-difluorophenyl)-3-hydroxypropionic acid (**compound 87C**)



Methyl 2-(2,4-difluorophenyl)-3-hydroxy-propionate (260 mg, 1.20 mmol) was dissolved in water (3 mL) and tetrahydrofuran (3 mL), and added with lithium hydroxide (100 mg, 2.38 mmol) at room temperature. After the addition was completed, the reaction system was placed and stirred at 25°C under nitrogen atmosphere for 2 hours. After the reaction was complete, the product was separated and purified through a silica gel column to obtain **compound 87C**.

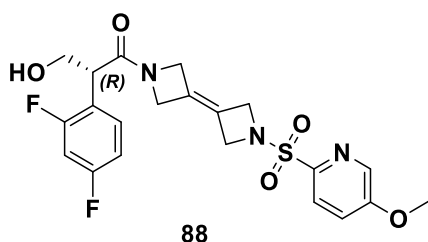
MS (ESI) m/z 201.0 (M-H)⁻.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-methoxypyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(2,4-difluorophenyl)-3-hydroxypropionic acid, and the same preparation method as that of Example 1 was adopted for separation to obtain **compound 87** of Example 87.

MS (ESI) m/z 466.1(M+H)⁺.

¹H-NMR (400 MHz, DMSO- *d*₆) δ 8.49-8.48 (d, *J* = 2.7 Hz, 1H), 7.96-7.34 (d, *J* = 8.8 Hz, 1H), 7.67-7.64 (m, 1H), 7.43-7.41 (m, 1H), 7.22-7.17 (m, 1H), 7.07-7.04 (m, 1H), 4.74-4.4.71 (d, *J* = 12.9 Hz, 1H), 4.48 (s, 4H), 4.36-4.21 (m, 3H), 3.94 (s, 3H), 3.89-3.83 (m, 2H), 3.55-3.48 (m, 1H).

Example 88: preparation of (*R*)-2-(2,4-difluorophenyl)-3-hydroxy-1-(1'-((5-methoxypyridin-2-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 88**):

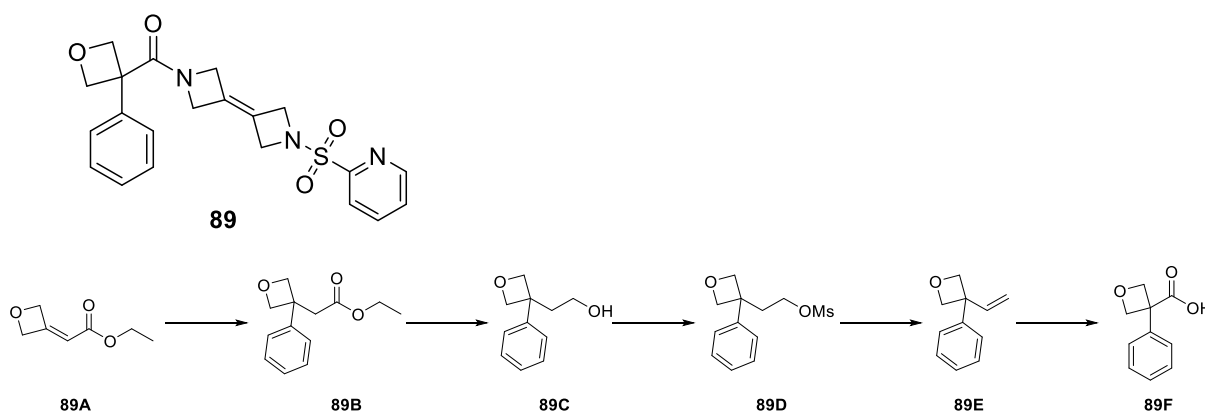


In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-methoxypyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((tert-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 2-(2,4-difluorophenyl)-3-hydroxypropionic acid, the same preparation method as that of Example 1 was adopted for separation, and then the product was subjected to chiral separation to obtain **compound 88** of Example 88.

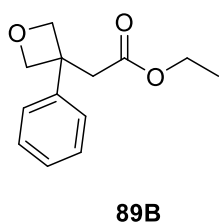
MS (ESI) m/z 466.1(M+H)⁺.

¹H-NMR (400 MHz, DMSO- *d*₆) δ 8.49-8.48 (d, *J* = 2.7 Hz, 1H), 7.96-7.34 (d, *J* = 8.8 Hz, 1H), 7.67-7.64 (m, 1H), 7.43-7.41 (m, 1H), 7.22-7.17 (m, 1H), 7.07-7.04 (m, 1H), 4.74-4.4.71 (d, *J* = 12.9 Hz, 1H), 4.48 (s, 4H), 4.36-4.21 (m, 3H), 3.94 (s, 3H), 3.89-3.83 (m, 2H), 3.55-3.48 (m, 1H).

Example 89: preparation of (3-phenyloxetan-3-yl)(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl) methanone (**compound 89**):



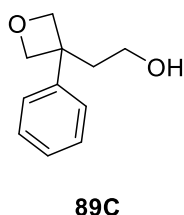
Step 1: preparation of ethyl 2-(3-phenyloxetan-3-yl)acetate (**compound 89B**)



- 5 Ethyl 2-(oxetan-3-ylidene)acetate (5 g, 35.17 mmol) was dissolved in 1,4-dioxane, and then sequentially added with an aqueous solution of potassium hydroxide (2.57 g, 1.5 N, 45.72 mmol), phenylboronic acid (6.43 g, 52.76 mmol) and chloro(1,5-cyclooctadiene)rhodium (I) dimer (1.73 g, 3.52 mmol). After the addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 89B**.
- 10

MS (ESI) m/z 221.1 ($M+H$)⁺.

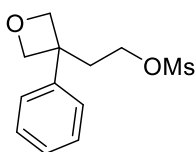
Step 2: preparation of 2-(3-phenyloxetan-3-yl)ethan-1-ol (**compound 89C**)



- 15 Ethyl 2-(3-phenyloxetan-3-yl)acetate (3 g, 13.62 mmol) was dissolved in a tetrahydrofuran solution, and the reaction system was cooled to 0°C, and then slowly added with lithium aluminum hydride (0.52 g, 13.62 mmol). After the addition was completed, the reaction was naturally warmed to room temperature and stirred for 2 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 89C**.

MS (ESI) m/z 179.1 ($M+H$)⁺.

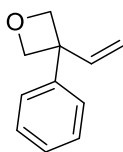
- 20 **Step 3:** preparation of 2-(3-phenyloxetan-3-yl)ethyl methanesulfonate (**compound 89D**)



89D

2-(3-phenyloxetan-3-yl)ethan-1-ol (2.43 g, 13.63 mmol) was dissolved in dichloromethane. The reaction system was cooled to 0°C, then added with triethylamine (2.48 g, 24.54 mmol), and then slowly added dropwise with methylsulfonyl chloride (2.81 g, 24.54 mmol). After the addition was completed, the reaction was naturally warmed to room temperature and stirred for 2 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 89D**.

Step 4: preparation of 3-phenyl-3-vinyloxetane (**compound 89E**)

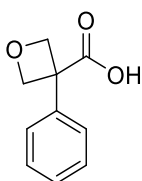


89E

2-(3-phenyloxetan-3-yl)ethyl methanesulfonate (3.4 g, 13.26 mmol) was dissolved in dimethyl sulfoxide, into which potassium *t*-butoxide (1.64 g, 14.59 mmol) was added in portions. After the addition was completed, the reaction system was stirred at room temperature for 16 hours. After the reaction was complete, the reaction system was added with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (200 mL*3). The organic phases were combined, and separated and purified through a silica gel column to obtain **compound 89E**.

MS (ESI) m/z 161.1 ($M+H$)⁺.

Step 5: preparation of 3-phenyloxetane-3-carboxylic acid (**compound 89F**)



89F

3-phenyl-3-vinyloxetane (1.4 g, 8.74 mmol) was dissolved in a mixed solution of ethyl acetate, acetonitrile and water. The reaction system was cooled to 0°C and added with ruthenium trichloride (91 mg, 0.43 mmol). After the addition was completed, the reaction was stirred at 0°C for 10 minutes, and then slowly added with sodium periodate (7.17 g, 33.21 mmol) in portions. After the addition was completed, the reaction was kept at 0°C and stirred for 30 minutes. After the reaction was complete, the reaction system was filtered through diatomite, the aqueous phase was extracted with ethyl acetate (200 mL*3), and the organic phases were combined, concentrated, then added with a saturated aqueous sodium bicarbonate, and extracted once with ethyl acetate. The aqueous phase was slowly added dropwise with 1N hydrochloric acid aqueous solution to adjust pH to 1, and spinned to dry to obtain

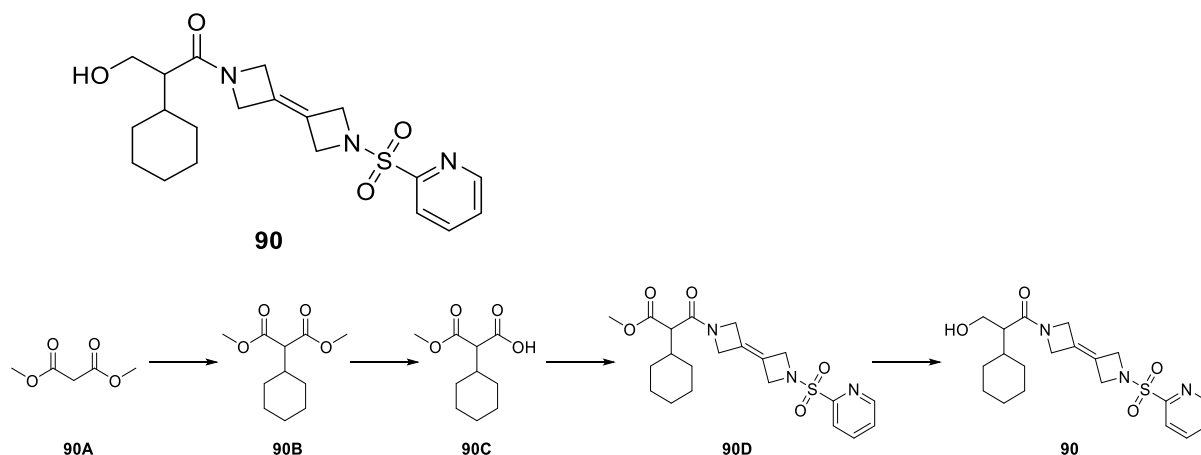
compound 89F.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by pyridine-2-sulfonyl chloride, and in step 10, (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-phenylpropionic acid was replaced by 3-phenyloxetane-3-carboxylic acid, the same preparation method as that of Example 1 was adopted for separation, and then the product was subjected to chiral separation to obtain **compound 89** of Example 89.

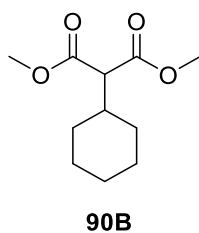
MS (ESI) m/z 412.1(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (m, 1H), 8.14 (m, 1H), 7.96 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.75 (m, 1H), 7.43 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.35 (m, 3H), 5.09 (d, *J* = 6.2 Hz, 2H), 4.69 (d, *J* = 6.2 Hz, 2H), 4.48 (m, 4H), 4.41 – 4.33 (m, 2H), 4.12 – 4.03 (m, 2H).

Example 90: preparation of 2-cyclohexyl-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 90**):



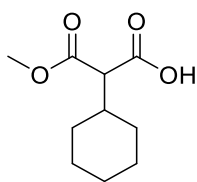
Step 1: preparation of dimethyl 2-cyclohexylmalonate (**compound 90B**)



Sodium (1.6 g, 71.41 mmol) was slowly added into anhydrous methanol (100.0 mL) in portions in ice bath. After the sodium wire was completely dissolved, dimethyl malonate (6.3 g, 47.61 mmol) and iodocyclohexane (10.0 g, 47.61 mmol) were added thereto. The reaction solution was reacted at 70°C for 18 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 90B**.

MS (ESI) m/z 215.3 (M+H)⁺.

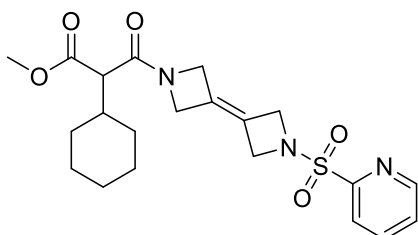
Step 2: preparation of 2-cyclohexyl-3-methoxy-3-oxopropionic acid (**compound 90C**)



90C

Dimethyl 2-cyclohexylmalonate (100.0 mg, 0.47 mmol) was dissolved in methanol (3.0 mL) and water (1.0 mL), and then added with an aqueous solution (1.0 mL) of potassium hydroxide (26.2 mg, 0.47 mmol). The reaction solution was stirred at room temperature for 3 hours. LCMS showed that the reaction was substantially completed. The reaction solution was adjusted to pH of 5 with 1N hydrochloric acid, and extracted with ethyl acetate (50 mL*3). The organic phases were combined, washed with a saturated brine, and dried over anhydrous sodium sulfate. It was concentrated to obtain a yellow oily compound, which was directly used in the next step of reaction.

Step 3: preparation of methyl 2-cyclohexyl-3-oxo-3-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propanoate (**compound 90D**)

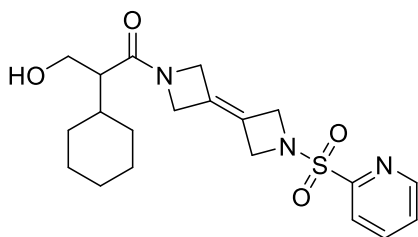


90D

2-cyclohexyl-3-methoxy-3-oxopropionic acid (93.4 mg, 0.46 mmol), 1-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-3,3'-diazetidinylidene (94.78 mg, 0.26 mmol), HATU (197.3 mg, 0.52 mmol) and *N,N*-diisopropylethylamine (134.1 mg, 1.04 mmol) were dissolved in *N,N*-dimethylformamide (5.0 mL). The reaction solution was stirred at room temperature for 3 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 90D**.

MS (ESI) m/z 434.2 ($M+H$)⁺.

Step 4: preparation of 2-cyclohexyl-3-hydroxy-1-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)propan-1-one (**compound 90**):



90

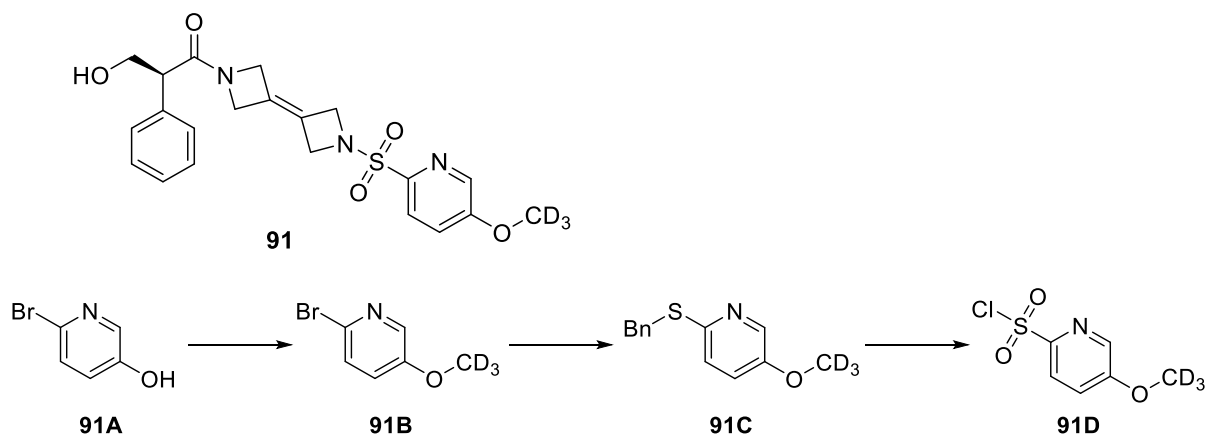
Methyl

2-cyclohexyl-3-oxo-3-(1'-(pyridin-2-ylsulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl) propionate (60.0 mg, 0.14 mmol) was dissolved in methanol (6.0 mL) and tetrahydrofuran (6.0 mL), and then added with sodium borohydride (52.4 mg, 1.38 mmol). The reaction solution was stirred at 80°C for 72 hours. After the reaction was complete, the product was separated and purified through reversed-phase high-pressure liquid chromatography to obtain **compound 90**.

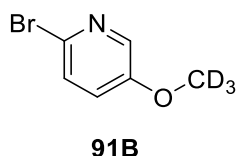
MS (ESI) *m/z* 406.2 (M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83-8.82 (d, *J* = 4.4 Hz, 1H), 8.19-8.17 (m, 1H), 8.00-7.98 (d, *J* = 8.0 Hz, 1H), 7.78-7.75 (m, 1H), 4.63-4.46 (m, 8H), 4.30-4.25 (m, 2H), 3.52-3.36 (m, 2H), 2.16-2.14 (m, 1H), 1.65-1.58 (m, 4H), 1.52-1.32 (m, 2H), 1.10-1.03 (m, 2H), 1.00-0.81 (m, 2H).

- 10 **Example 91:** preparation of (S)-3-hydroxy-1-(1'-((5-(methoxy-*d*₃)pyridin-2-yl)sulfonyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)-2-phenylpropan-1-one (**compound 91**):



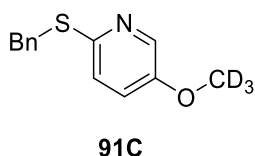
- 15 **Step 1:** preparation of 2-bromo-5-(methoxy-*d*₃)pyridine (**compound 91B**)



- 20 2-bromo-5-hydroxypyridine (3 g, 17.24 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with deuterated methanol (3.11 g, 86.20 mmol), triphenylphosphine (4.97 g, 18.96 mmol) and DIAD (3.83 g, 18.96 mmol). After the addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 91B**.

MS (ESI) *m/z* 191.0 (M+H)⁺.

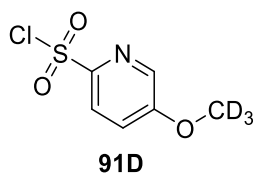
Step 2: preparation of 2-(benzylthio)-5-(methoxy-*d*₃)pyridine (**compound 91C**)



2-bromo-5-(methoxy-*d*₃)pyridine (2.53 g, 13.24 mmol) was dissolved in 1,4-dioxane solution, and then sequentially added with benzyl mercaptan (1.64 g, 13.24 mmol), DIPEA (3.42 g, 26.49 mmol), Pd₂(dba)₃CHCl₃ (1.35 g, 1.32 mmol) and xantphos (1.53 g, 2.65 mmol). After the addition was completed, the reaction was replaced under nitrogen environment for 3 times, then heated to 80°C, and stirred for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 91C**.

MS (ESI) *m/z* 235.1 (M+H)⁺.

Step 3: preparation of 5-(methoxy-*d*₃)pyridine-2-sulfonyl chloride (**compound 91D**)



2-(benzylthio)-5-(methoxy-*d*₃)pyridine (1.1 g, 4.69 mmol) was dissolved in acetonitrile, into which acetic acid (1.41 g, 23.47 mmol), water (846 mg, 46.94 mmol) and 1,3-dichloro-5,5-dimethylhydantoin (1.85 g, 9.39 mmol) were sequentially added. After the addition was completed, the reaction was stirred at room temperature for 16 hours. After the reaction was complete, it was separated and purified through a silica gel column to obtain **compound 91D**.

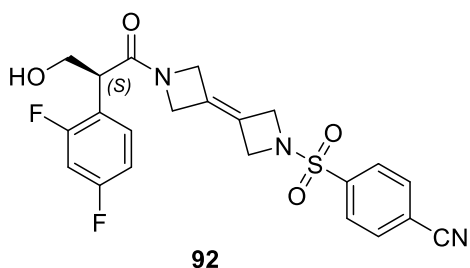
MS (ESI) *m/z* 211.0 (M+H)⁺.

In step 8 of Example 1, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridine-7-sulfonyl chloride was replaced by 5-(methoxy-*d*₃)pyridine-2-sulfonyl chloride, and the same preparation method as that of Example 1 was adopted for separation to obtain **compound 91** of Example 91.

MS (ESI) *m/z* 433.2(M+H)⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 2.9 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.64 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.27 (m, 5H), 4.80 (t, *J* = 5.2 Hz, 1H), 4.72 (d, *J* = 13.4 Hz, 1H), 4.48 (s, 4H), 4.41 – 4.27 (m, 2H), 4.21 (d, *J* = 14.7 Hz, 1H), 3.89 (m, 1H), 3.62 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.46 (m, 1H).

Example 92: preparation of *(S)*-4-((1'-(2-(2,4-difluorophenyl)-3-hydroxypropyl)-1',4'-dihydro-2*H*,2'*H*-[3,3'-diazetidinylidene]-1(4*H*)-yl)sulfonyl)benzonitrile (**Compound 92**):



In step 3 of Example 35, 4-cyanobenzenesulfonyl chloride was substituted for 2-methylbenzo[*d*]thiazole-6-sulfonyl chloride, and in step 5, *(S)*-2-(2,4-difluorophenyl)-3-hydroxypropionic acid was substituted for *(S)*-3-hydroxy-2-phenylpropionic acid. **Compound 92** of Example 92 was isolated using the same

preparation method as in Example 35.

MS (ESI) m/z 460.1(M+H)⁺

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H), 7.41 (m, 1H), 7.20 (m, 1H), 7.04 (m, 1H), 4.91 (t, J = 5.0 Hz, 1H), 4.70 (d, J = 12.5 Hz, 1H), 4.40 – 4.27 (m, 6H), 4.21 (d, J = 13.4 Hz, 1H), 3.85 (d, J = 5.3 Hz, 2H), 3.61 – 3.46 (m, 1H).

Biological test data

Unless otherwise specified, all of the test materials, reagents, operations and methods used in the following activity examples are commercially available or can be easily known or prepared based on the prior art.

Test Example 1: pyruvate kinase (PKR) activity test

1. Experimental objective

To test the activation effect of the compound of the present disclosure on recombinant human PKR.

2. Experimental materials and instruments

Reagents and consumables:

Reagent Name	Supplier	Cat. No.
PKLR Var2 active human	Sigma-Aldrich	9001-59-6
DMSO	Xiya reagent	20190701
Pyruvate Kinase Assay Kit	Abcam	ab83432

Instrument:

Instrument name	Factory	Model
Multifunctional microplate reader	BMG	PERAstar® FSX

3. Test steps:

3.1 A recombinant human PKR enzyme solution was prepared at a concentration of 60 ng/well (a 20 μ L reaction system), and 5 μ L of the solution was added into each well of a black transparent bottom 384-well plate.

3.2 Compound solutions were prepared at different concentrations, with the final concentrations of 1000/300/100 nM (containing 1% DMSO). Each 5 μ L of the compound solution was added into the plate in step 3.1 and mixed well. The plate was incubated at room temperature for 10 min.

3.3 A reaction system was prepared according to the instructions of a kit (as shown in the table below), and 10 μ L of the reaction system was added into each well of the 384-well plate, and mixed uniformly with the solution in step 3.2.

Item	μ L
------	---------

OxiRed™ Probe	0.08
HRP Enzyme Mix (Lyophilized)	0.2
PK Substrate Mix (Lyophilized)	0.4
PK Assay Buffer	9.32

3.4 The 384-well plate was placed on a microplate reader to detect the fluorescence value at 540/590 nm, where the value was read every 2 minutes and the detection was conducted continuously for 1 hour.

3.5 The Slope value within the detection time was calculated, and the 1% DMSO well was used as a control well to calculate a compound activation rate.

5
$$\text{Activation rate \%} = (\text{Slope of compound well} / \text{Slope of control well}) \times 100\%$$

3.6 Fitting dose-effect curve

With the log value of the compound concentration as the X axis and the percentage activation rate as the Y axis, a dose-effect curve was fitted with the log(agonist) vs. response-variable slope of the analysis software GraphPad Prism 5, and the AC₅₀ value of the activity of each compound against PKR was obtained.

10 Calculation formula:
$$Y = \min + (\max - \min) / (1 + 10^{((\text{LogAC}_{50} - X) \times \text{Hillslope}))}$$

4. Test results:

The activation effects of the compounds of the present disclosure on PKR enzyme were determined through the aforementioned tests, and the determined AC₅₀ values were as follows (A represented 0-100 nM, B represented 101-300 nM, and C represented 300-1,000 nM).

15

Compound	AC ₅₀	Compound	AC ₅₀	Compound	AC ₅₀
1	C	32	A	63	B
2	A	33	C	64	C
3	A	34	C	65	B
4	B	35	A	66	B
5	A	36	C	67	A
6	A	37	A	68	C
7	B	38	C	69	A
8	C	39	A	70	C
9	B	40	B	71	A
10	B	41	C	72	A
11	B	42	C	73	B
12	A	43	C	74	A

13	A	44	A	75	B
14	B	45	A	76	C
15	C	46	A	77	A
16	B	47	C	78	C
17	C	48	B	79	A
18	A	49	A	80	A
19	B	50	A	81	B
20	B	51	C	82	A
21	C	52	C	83	A
22	C	53	C	84	C
23	C	54	A	85	C
24	C	55	C	86	C
25	A	56	C	87	A
26	A	57	B	88	C
27	C	58	B	89	B
28	C	59	B	90	B
29	A	60	C	91	A
30	A	61	C		
31	C	62	C		

Test Example 2: ex vivo pyruvate kinase (PKR) activity experiment

1. Experimental objective

5 To test the effects of the compound of the present disclosure on PKR activation in ex vivo red blood cells from healthy individuals and patients with thalassemia.

2. Experimental materials and instruments

Main reagents and consumables

Reagent name	Supplier/Source	Cat. No.
Healthy human peripheral blood	Healthy volunteers	
Peripheral blood of patients with thalassemia	patients with	

	thalassemia	
EDTA-K2 anticoagulant tube	BD	367525
Red blood cell lysis buffer	Beyotime Biotechnology	C3702
DMSO	Sigma	D8418
Fetal Bovine Serum	Excell Bio	FSP500
1×PBS	gibco	C10010500CP
10×PBS	Solarbio	P1022
Adenine	Sigma	A2786
D-Mannitol	Sigma	M1902
D-glucose (anhydrous)	Aladdin	D274366
Percoll cell separation solution	solarbio	P8370
Penicillin-Streptomycin	HyClone	sv30010
Pyruvate Kinase Assay Kit	Abcam	ab83432

Instruments:

Instrument name	Factory	Model
Multifunctional microplate reader	BMG	PERAstar® FSX
CO ₂ incubator	Thermo	371
Centrifuge	Effpendorf	5430

3. Test steps

a) Preparation of AGAM medium

- 5 i. 5 g of glucose, 85 mg of adenine, and 2.625 g of mannitol were weighed and added into a 50 mL centrifuge tube. 40 mL of PBS was added to dissolve (sonicate for 30 minutes until completely dissolved). The solution was filtered through a 0.22 µm filter, then added to 460 mL of sterile PBS and mixed thoroughly.

b) Isolation, purification, and storage of red blood cells

- 10 i. Fresh human peripheral blood was collected. K₂EDTA was used as the anticoagulant. 1 part anticoagulant with 9 parts blood was mixed, then centrifuged at 500 g for 10 minutes at room temperature to remove the plasma.
- ii. Packed red blood cells: 1.5 volumes of PBS were added, then centrifuged at 2000 ×g for 5 minutes at room temperature. After centrifugation, the supernatant was removed. This step was repeated twice.
- iii. Diluted red blood cells: 1.5 volumes of PBS were added, then resuspended and mixed thoroughly.

iv. The diluted red blood cells were slowly added to 0.5 volume of 70% isotonic solution (e.g., 7.5 mL of diluted red blood cells + 3 mL of 70% isotonic solution Percoll) and centrifuged at 4000 ×g for 20 minutes at 4°C.

5 v. The supernatant was removed. The red blood cells at the bottom were washed once with 4-5 mL of PBS to elute the Percoll gel, and then centrifuged at 2000 ×g for 5 minutes at room temperature.

vi. The supernatant was removed. The red blood cells were counted and then diluted in AGAM medium containing 10% FBS to a density of 2×10^8 cells/mL for storage at 4°C.

c) Agonist Activity Assay

10 i. The red blood cells were seeded into a 96-well plate at a uniform density of 1×10^7 cells/mL, with 100 µL per well. The test compounds (dissolved in DMSO) were diluted and added to the cell culture medium, resulting in final compound concentrations of 3000, 1000, 300, 100, 10, 3, and 1 nM (with 1% DMSO). The cells and compounds were co-cultivated for 3 hours in a 37°C incubator with 5% CO₂. Subsequently, the plate was centrifuged at 2000 g for 20 minutes, and the supernatant was discarded. 100 µL of red blood cell lysis buffer was added to the cell pellet, vortexed for 20 minutes, and
15 centrifuged at 4000 g for 5 minutes. The supernatant was collected for analysis.

ii. The reaction system was prepared according to the kit instructions (shown as the table below), 10 µL of the reaction system was added to each well of a 384-well plate, and 10 µL of red blood cell lysis buffer was took and mixed well (20 µL reaction system).

Item	µL
OxiRed™ Probe	0.08
HRP Enzyme Mix (Lyophilized)	0.2
PK Substrate Mix (Lyophilized)	0.4
PK Assay Buffer	9.32

20 iii. A black, transparent-bottomed 384-well plate was placed in a microplate reader to measure fluorescence at 540/590 nm. The fluorescence was read every 2 minutes for 1 hour.

d) Data Analysis

i. The Slope value was calculated over the assay time. Compound activation percentage was calculated using the 1% DMSO well as the control well. Activation percentage = (Slope of compound well / Slope
25 of control well) × 100%

ii. Dose-response curve was fit using the logarithmic compound concentration on the X-axis and the percent activation percentage on the Y-axis, the log(agonist) vs. response - variable slope function in GraphPad Prism 5 was used to determine the AC₅₀ value for each compound on PKR activity.

Calculation formula: $Y = \min + (\max - \min) / (1 + 10^{((\text{LogAC}_{50} - X) \times \text{Hillslope}))}$.

30 The PKR agonist effects of the compound of the present disclosure on ex vivo red blood cells from healthy individuals and thalassemia patients were determined using the above assay. The AC₅₀ values

measured on ex vivo red blood cells from healthy individuals are as follows (A represents 0-100 nM, B represents 101-300 nM, and C represents 300-1000 nM):

Compound	AC ₅₀	Compound	AC ₅₀	Compound	AC ₅₀
1	B	32	A	63	C
2	C	33	C	64	C
3	B	34	C	65	A
4	A	35	A	66	A
5	B	36	A	67	A
6	B	37	C	68	B
7	A	38	C	69	A
8	A	39	A	70	B
9	A	40	C	71	B
10	A	41	A	72	A
11	A	42	C	73	B
12	C	43	B	74	A
13	A	44	A	75	B
14	B	45	A	76	C
15	C	46	A	77	A
16	A	47	C	78	C
17	C	48	C	79	B
18	A	49	A	80	A
19	C	50	A	81	C
20	C	51	C	82	B
21	A	52	C	83	A
22	A	53	B	84	C
23	C	54	A	85	C
24	C	55	C	86	C
25	C	56	C	87	A
26	C	57	A	88	C

27	C	58	B	89	A
28	C	59	A	90	C
29	A	60	C	91	A
30	A	61	B		
31	C	62	C		

The AC₅₀ values of ex vivo red blood cells of patients with thalassemia are as follows:

Compound	AC ₅₀ (nM)			
	Patient A	Patient B	Patient C	Patient D
65	250.7	84.4	139.6	144.8
83	21.8	20.9	24.8	11.7

The experimental data show that the compound of the present disclosure has agonistic activity on PKR in ex vivo red blood cells of healthy individuals and thalassemia patients.

5

Test Example 3: in vivo efficacy study in wild-type mice

1. Experimental objective

The effects of the compound on wild-type mice were evaluated by detecting the concentrations of HGB, ATP, and 2,3-DPG in the whole blood of mice.

10 2. Experimental animal

Strain	Gender/Age	Source
C57BL/6J	Female/Male/8 weeks old	GemPharmatech

3. Experimental procedures

a) Drug preparation

i. On the day of administration, the compound was weighed, then the vehicle was added to prepare the administration solution:

15 vehicle: 5% DMSO + 10% Solutol + 85% Saline

b) Grouping and administration

i. Wild-type mice were randomly divided into groups based on body weight, with 8 mice per group. Administration was performed according to the schedule shown in the table below.

Animal strain	Group	Dose (mg/kg)	Administration route	Administration frequency	Administration days
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C57BL/6J	Compound 65	2.5	Oral gavage	Twice a day	14 days
		7.5			
		25			
	Compound 83	15			
		50			
		75			

c) Determination of HGB content in Mice

i. Whole blood sample was collected 2-3 hours after the last administration of the test animal for HGB assay.

d) Determination of ATP and 2,3-DPG contents in the whole blood of mice

- 5 i. An LC-MS/MS method was established to determine the ATP and 2,3-DPG contents in whole blood sample 2-3 hours after the last administration of the test animal.

The compound of the present disclosure was assayed using the above assay. The measured hemoglobin ATP and 2,3-DPG concentrations in wild-type mice after administration are shown in the table below.

Animal strain	Group	Dose (mg/kg)	HGB (g/dL)	ATP (μg/mL)	2,3-DPG (μg/mL)
C57BL/6J	Vehicle control	0	14.9	452.0	1727.8
	Compound 65	2.5	15.1	481.5	1417.4
		7.5	14.9	486.5	1417.4
		25	14.9	475.9	1363.0
	Compound 83	15	15.3	476.9	1454.1
		50	15.4	472.1	1444.5
		75	14.6	474.1	1441.8

10 **Test Example 4: Pharmacokinetic properties test in mice, rats, and dogs**

1. Experimental objective

The pharmacokinetic properties of the compounds of the present disclosure in different animal species were investigated by measuring plasma drug concentrations following intravenous and oral gavage in mouse, rat, and dog.

15 **2. Experimental animals**

Strain/Grade	Gender	Source
--------------	--------	--------

ICR mouse / SPF grade	Male	Bikai Keyi Biotechnology (Shanghai)
SD rat / SPF grade	Male	Shanghai Xipu-Bikai Laboratory Animal Co., Ltd.
Beagle/General	Male	

3. Experimental procedures

a) Drug preparation and administration

i. The compounds were weighed, then the solvent (5% DMSO + 10% Solutol + 85% saline) was added to prepare the administration solution.

5 ii. On the day before the experiment, animals in the oral administration group were fasted overnight (10-14 hours) and fed 4 hours after administration.

iii. On the day of the experiment, administration was performed according to the schedule shown in the table below. At each time point after administration, approximately 30 μ L of venous blood was collected from an appropriate location in each group of animals and placed in a sodium heparin tube.

10 Blood samples were placed on ice and centrifuged within 1 hour to separate plasma (centrifugation conditions: 6800 g, 6 min, 2-8°C). Plasma samples were stored at -80°C until analysis.

Animal strain	Dose (mg/kg)	Volume (mL/kg)	Concentration (mg/mL)	Administration route	Administration frequency	Fasting or not	Sample collection time
ICR mouse/ SD rat	1	5	0.2	Intravenous injection	Single	Yes	5, 15, 30 min, 1, 2, 4, 8, 24 h after administration
ICR mouse/ SD rat	10	10	1	Oral gavage	Single	Yes	5, 15, 30 min, 1, 2, 4, 8, 24 h after administration
Beagle	2	2	1	Intravenous injection	Single	Yes	5, 15, 30 min, 1, 2, 4, 8, 24 h after administration
Beagle	5	5	1	Oral gavage	Single	Yes	5, 15, 30 min, 1, 2, 4, 8, 24 h after administration

b) An LC-MS/MS analytical method was developed for measuring compound concentrations in mouse, rat, and dog plasma. This method was used to determine compound concentrations in biological samples obtained in this assay.

15 c) Data analysis

Pharmacokinetic parameters were calculated using Phoenix WinNonlin 7.0 using plasma drug concentration data at different time points.

The compounds of the present disclosure was tested using the above assay. The pharmacokinetic parameters measured in different animal species are shown in the table below.

The results demonstrate that the compounds of the present disclosure are well absorbed orally in rat, mouse, and dog.

Compound	Specie	Dose (mg/kg)	T _{1/2} (h)	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-t} (h*ng/mL)	MRT _{0-t} (h)	V _{ss} (mL/kg)	CL (mL/h/kg)
65	ICR mouse	1	1.30	0.08	945	679	0.91	1,497	1,507
		10	1.75	0.33	4,226	7,880	1.89	/	/
	SD rat	1	0.64	0.08	688.54	394.05	0.58	1562.40	2529.58
		10	1.53	0.25	993.26	1730.79	2.24	/	/
	Beagle	2	5.81	0.14	1,766	8,571	5.53	1552	223
		5	4.47	1.33	2,480	19,480	5.28	/	/
83	ICR mouse	1	2.44	0.08	570	260	1.33	6,296	3,772
		10	2.03	0.25	1,439	2,011	1.71	/	/
	SD rat	1	4.91	0.08	730.85	536.70	2.12	5105.06	1793.23
		10	3.43	0.25	1737.38	3302.95	3.20	/	/
	Beagle	2	3.72	0.08	1,594	3,110	2.79	1931	670
		5	5.21	0.67	3,305	12,192	4.51	/	/

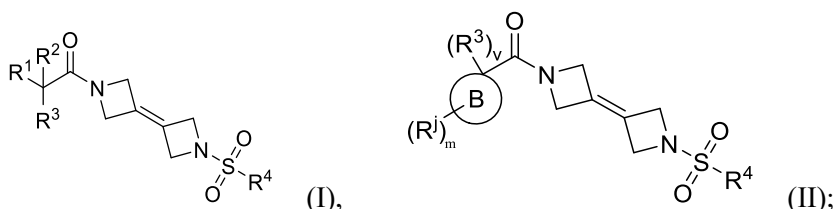
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The present disclosure is not limited to the aforementioned optional embodiments, and anyone can derive various other forms of products under the motivation of the present disclosure. The aforementioned specific embodiments should not be understood as limiting the scope of the present disclosure. The protection scope of the present disclosure should be subjected to the definitions of the claims, and the specification can be used for interpreting the claims.

10

What is claimed is:

1. Use of a pharmaceutical composition in the preparation of a medicament for preventing or treating anemia-related disease, wherein the pharmaceutical composition comprises an active ingredient and a pharmaceutically acceptable excipient, the active ingredient is a compound of the following formula I or II, or an isomer, pharmaceutically acceptable salt or solvate thereof, and the content of the active ingredient in the pharmaceutical composition is 0.05 mg to 1000 mg:



wherein,

R^1 , R^2 and R^3 are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b, -SR^b, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f or -C(O)OR^g, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -SR^b, -NO₂, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f and -C(O)OR^g;

or, R^1 and R^2 , R^1 and R^3 , or R^2 and R^3 together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, -(C₅-C₈)spirocyclyl, 5-8 membered spiroheterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, or 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S;

R^4 is -NH₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b, -SR^b, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f, -C(O)OR^g or -NR^c(CR^hRⁱ)_t-R^a, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -SR^b, -NO₂, -NR^cR^d, -S(O)₂R^e, -S(O)₂NR^cR^d, -S(O)R^e, -S(O)NR^cR^d, -NR^cS(O)₂R^e, -NR^cS(O)R^e, -C(O)R^f and -C(O)OR^g;

t is 0, 1, 2 or 3;

R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h and R^i at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14

membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH, -NHS(O)OH, -C(O)H or -C(O)OH, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H, -C(O)OH, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, and 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

or, any two groups on adjacent atoms selected from R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and Rⁱ together with atoms to which they are attached optionally bind to form C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, (C₃-C₈)cycloalkyl, or 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, which is optionally substituted by one or more R^a;

wherein in formula II:

each Rⁱ is independently -H, halogen, -OH, -NH₂, -CN, =O, -NO₂, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH, -NHS(O)OH, -C(O)H or -C(O)OH, wherein each of the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -H, =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH, -NHS(O)OH, -C(O)H, -C(O)OH, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, or 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S;

m is independently selected from 0, 1, 2, 3, 4, 5 or 6;

v is 0 or 1;

ring B is (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S.

2. The use according to claim 1, wherein the anemia-related disease is pyruvate kinase deficiency (PKD).

3. The use according to claim 1, wherein the anemia-related disease comprises myelodysplastic

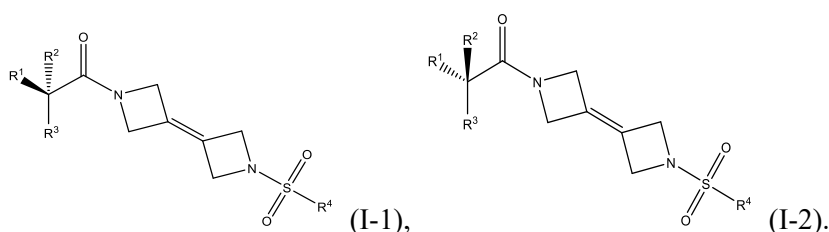
syndrome (MDS), hemoglobinopathy, sickle cell anemia (SCD), β -thalassemia, hereditary non-spherocytic hemolytic anemia, hemolytic anemia, hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, paroxysmal nocturnal hemoglobinuria, acquired hemolytic anemia, congenital anemia or anemia of chronic disease.

5

4. The use according to claim 1, wherein the anemia-related disease is sickle cell anemia (SCD), β -thalassemia or lower-risk myelodysplastic syndrome (LR-MDS).

5. The use according to claim 1, wherein a unit dose of the pharmaceutical composition comprises 0.05
10 mg to 1000 mg of active ingredient.

6. The use according to claim 1, wherein the compound of formula I has the structure shown in formula I-1 or I-2:



15

7. The use according to claim 1, wherein

R^1 and R^2 are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b or -NR^cR^d, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

25 or, R^1 and R^2 together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

R^a , R^b , R^c , and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, and 3-14 membered heterocyclyl containing 1-4
35 heteroatoms independently selected from O, N and S.

8. The use according to claim 7, wherein

R¹ and R² are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b or -NR^cR^d, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

or, R¹ and R² together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, and 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S.

9. The use according to claim 8, wherein

R¹ and R² are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆) linear alkyl, -(C₁-C₆) branched alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 7-14 membered bicyclic or tricyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -OR^b or -NR^cR^d, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a, -OR^b, and -NR^cR^d;

or, R¹ and R² together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, or 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, and -(C₁-C₆)alkyl.

10. The use according to claim 9, wherein

R¹ and R² are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆) linear alkyl, -(C₁-C₆) branched alkyl, -(C₃-C₆)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is

optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a, -OR^b, and -NR^cR^d;

or, R¹ and R² together with atoms to which they are attached optionally bind to form -(C₃-C₈)cycloalkyl or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S;

- 5 R^a, R^b, R^c, and R^d at each occurrence are independently -H, -F, -Cl, -Br, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, and -(C₁-C₆)alkyl.

10

11. The use according to claim 10, wherein

R² is -H, -F, -Cl or -Br;

R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, -(CH₂)_qCH₃, -(CH₂)_qOH, -CH(OH)(CH₂)_qCH₃, -C(OH)((CH₂)_qCH₃)₂,
HO-, -(CH₂)_qNH₂, -(CH₂)_qNH(CH₂)_qCH₃, -(CH₂)_qN((CH₂)_qCH₃)₂, 3-6 membered heterocycloalkyl
15 containing 1 N atom, or -(C₁-C₆)alkyl substituted by 3-6 membered heterocycloalkyl containing 1 N atom;

q at each occurrence is independently 0, 1, 2, 3 or 4;

or, R¹ and R² together with atoms to which they are attached optionally bind to form a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, tetrahydrofuran, tetrahydropyran,
20 morpholine, dioxane, 2,3-dihydrobenzofuran ring, or tetrahydro-2H-pyran.

12. The use according to claim 9, wherein

R² is -H, -F, -Cl or -Br;

- 25 R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, -CH₃, -CH(OH)CH₃, -(CH₂)_qCH₃, -(CH₂)_qOH, -CH(OH)(CH₂)_qCH₃, -C(OH)((CH₂)_qCH₃)₂, -C(OH)((CH₂)_qCH₃)(CH₃), -C(OH)(CH₃)₂, HO-, HO-, -CH₂F, -CHF₂, -(CH₂)_qCH₂F, -(CH₂)_qCHF₂, -CH₂Cl, -CHCl₂, -(CH₂)_qCH₂Cl, -(CH₂)_qCHCl₂, -(CH₂)_qNH₂, -NHCH₃, -NH(CH₂)_qCH₃, -(CH₂)_qNHCH₃, -(CH₂)_qNH(CH₂)_qCH₃, -N(CH₃)₂, -N((CH₂)_qCH₃)₂, -(CH₂)_qN(CH₃)((CH₂)_qCH₃), -(CH₂)_qN(CH₃)₂, -(CH₂)_qN((CH₂)_qCH₃)₂, 3-6 membered heterocycloalkyl containing 1 N atom, or -(C₁-C₆)alkyl substituted by 3-6 membered heterocycloalkyl containing 1 N atom;
30

q at each occurrence is independently 1, 2, 3 or 4;

or, R¹ and R² together with atoms to which they are attached optionally bind to form a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, oxetane, tetrahydrofuran, tetrahydropyran, morpholine, dioxane, 2,3-dihydrobenzofuran ring, or tetrahydro-2H-pyran.

35

13. The use according to claim 7, wherein

R² is -H, -F, -Cl or -Br;

R¹ is -H, -F, -Cl, -Br, -OH, -NH₂, , , , , , , , , ,  or .

or, R¹ and R² together with atoms to which they are attached optionally bind to form ,  or .

14. The use according to any one of claims 1-13, wherein

R³ is -H, halogen, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, and 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S.

15. The use according to claim 14, wherein

R³ is -H, halogen, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered bicyclic or tricyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -R^a, -OR^b, -NO₂, and -NR^cR^d;

R^a, R^b, R^c, and R^d at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₈ aryl, 5-8 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -NO₂, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, and 3-6

membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S.

16. The use according to claim 15, wherein

5 R^3 is -H, -F, -Cl, -Br, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, C₆-C₈ aryl, or 7-14 membered bicyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl, aryl or fused ring group is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -R^a and -OR^b;

10 R^a and R^b at each occurrence are independently -H, halogen, -OH, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₃-C₈)cycloalkyl, or 3-6 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, wherein each of the alkyl, cycloalkyl or heterocyclyl is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, and -(C₁-C₆)alkyl.

17. The use according to claim 14, wherein

R^3 is -H, -F, -Cl, -Br, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, pyridyl, phenyl, naphthyl, benzothiazolyl,

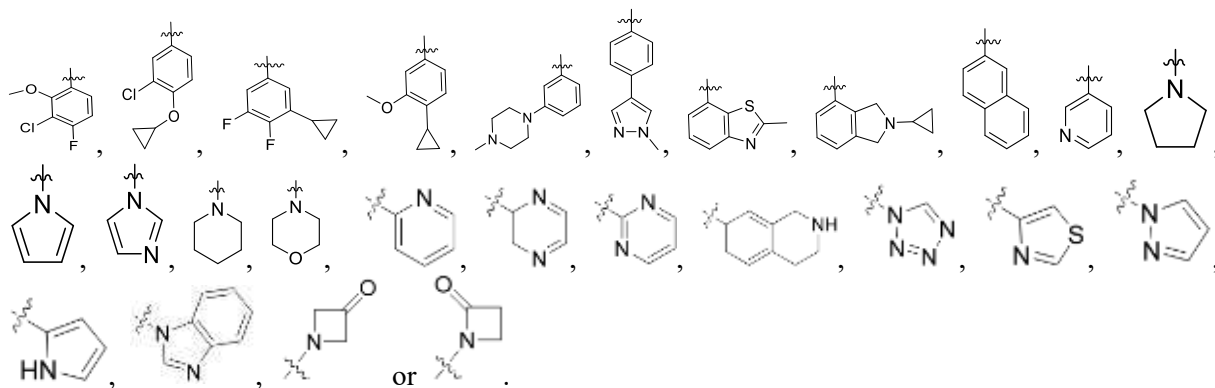
15 benzomorpholinyl, benzopyrrolidinyl or , wherein the pyridyl, phenyl, benzothiazolyl,

benzomorpholinyl, benzopyrrolidinyl, or  is optionally substituted by one or more substituents selected from: -F, -Cl, -Br, -CN, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, -O-(C₁-C₆)alkyl, -O-(C₃-C₆)cycloalkyl, -(C₁-C₆)haloalkyl, -(C₃-C₆)halocycloalkyl, -O-(C₁-C₆)haloalkyl, -O-(C₃-C₆)halocycloalkyl, pyrazolyl, pyrazolyl substituted by any number of halogen or -(C₁-C₆)alkyl, 20 piperazinyl, piperazinyl substituted by any number of halogen or -(C₁-C₆)alkyl;

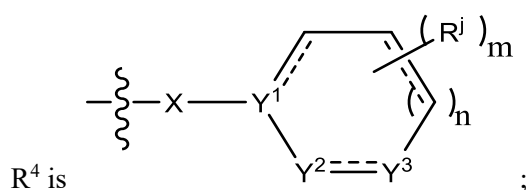
the ring  is 3-6 membered saturated or unsaturated N-containing heterocyclyl connected through an N atom, and in addition to the N atom, the heterocyclyl optionally contains 1-2 heteroatoms independently selected from O, N and S.

25 18. The use according to claim 14, wherein

R^3 is -H, -F, -Cl, -Br, -CH₃, -CH₂CH₃, , , , , , , , , , , , , , , , , , , , , , , , 



5 19. The use according to any one of claims 1-18, wherein



X is a chemical bond, $-(CR^hR^i)_t-$, $-NR^c(CR^hR^i)_t-$ or $-O-$;

===== represents a single bond or double bond;

Y^1 is N, C or CH;

10 Y^2 and Y^3 are each independently N, CH_2 or CH, and Y^2 and Y^3 are not both N at the same time;

each R^j is independently -H, halogen, -OH, -NH₂, -CN, -NO₂, $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkoxy$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_3-C_8)cycloalkyl$, $-O-(C_3-C_6)cycloalkyl$, $-(C_4-C_8)cycloalkenyl$, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C_6-C_{14} aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH, -NHS(O)OH, -C(O)H, or -C(O)OH, wherein each of the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: -H, =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH, -NHS(O)OH, -C(O)H, -C(O)OH, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C_6-C_{14} aryl, or 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S;

m is selected from 0, 1, 2, 3, 4, 5 or 6;

25 n is 0, 1 or 2,

R^c , R^h , R^i and t are as defined in any one of claims 1-18.

20. The use according to claim 19, wherein

X is a chemical bond, -CH₂-, -CH₂CH₂-, -NHCH₂-, -NHCH₂CH₂- or -O-;

===== represents a single bond or double bond;

Y¹ is N, C or CH;

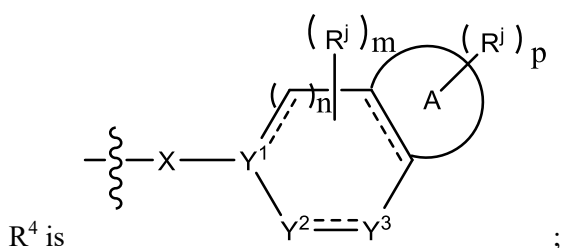
Y² and Y³ are each independently N, CH₂ or CH, and Y² and Y³ are not both N at the same time;

- 5 each Rⁱ is independently -H, halogen, -OH, -NH₂, -CN, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, -(C₁-C₆)alkoxy, -O-(C₃-C₆)cycloalkyl, -(C₁-C₆)alkyl substituted by any number of halogen, -(C₁-C₆)alkoxy substituted by any number of halogen, -(C₃-C₆)cycloalkyl substituted by any number of halogen, -O-(C₃-C₆)cycloalkyl substituted by any number of halogen, oxazolyl, thiazolyl and triazolyl;

m is selected from 0, 1, 2, 3, 4, 5 or 6;

- 10 n is 0, 1 or 2.

21. The use according to any one of claims 1-18, wherein



X is a chemical bond, -(CR^hRⁱ)_t-, -NR^c(CR^hRⁱ)_t- or -O-;

- 15 ===== represents a single bond or double bond;

Y¹ is N, C or CH;

Y² and Y³ are each independently N, CH₂ or CH, and Y² and Y³ are not both N at the same time;

- each Rⁱ is independently -H, halogen, -OH, =O, -NH₂, -CN, -NO₂, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S, -SH, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -S(O)₂OH, -S(O)OH, -NHS(O)₂OH, -NHS(O)OH, -C(O)H, or -C(O)OH, wherein each of the alkyl, alkoxy, alkenyl, alkynyl, 20 cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl or fused ring group is optionally substituted by one or more substituents selected from: =O, halogen, -CN, -OH, -SH, -NO₂, -NH₂, -S(O)₂H, -S(O)₂NH₂, -S(O)H, -S(O)NH₂, -NHS(O)₂H, -NHS(O)H, -C(O)H, -C(O)OH, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, or 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S;

- 30 m and p are independently selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

ring A is (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered fused ring group containing 0-4 heteroatoms independently selected from O, N and S;

5 R^c, R^h, R^i and t are as defined in any one of claims 1-18.

22. The use according to claim 21, wherein

X is a chemical bond, -CH₂-, -CH₂CH₂-, -NHCH₂-, -NHCH₂CH₂- or -O-;

===== represents a single bond or double bond;

10 Y^1 is N, C or CH;

Y^2 and Y^3 are each independently N, CH₂ or CH, and Y^2 and Y^3 are not both N at the same time;

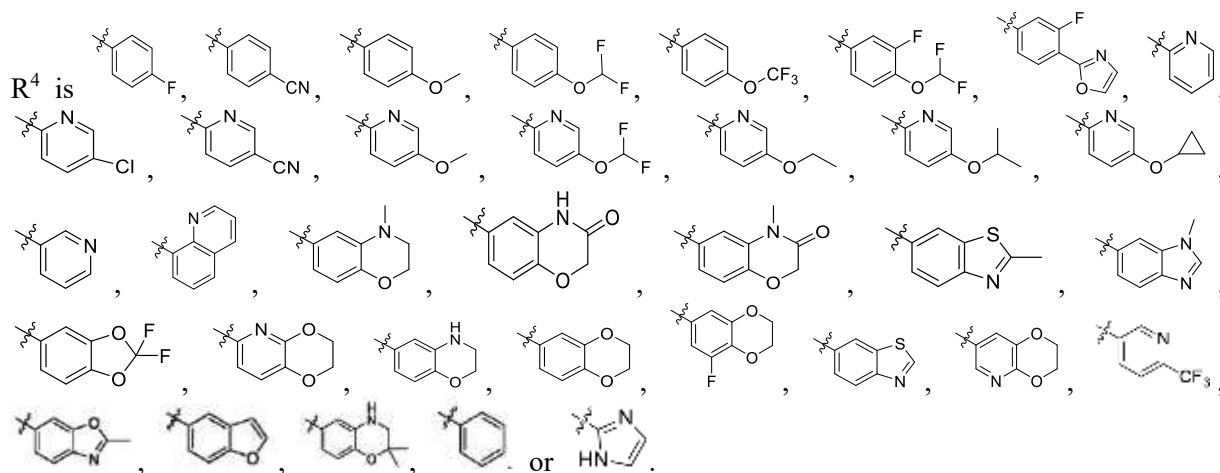
each R^j is independently -H, halogen, -OH, -NH₂, -CN, =O, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkyl substituted by any number of halogen, -(C₁-C₆)alkoxy substituted by any number of halogen, oxazolyl, thiazolyl, or triazolyl;

15 m and p are independently selected from 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

the ring A is furan, thiophene, oxazole, thiazole, triazole, piperidine, pyridine, pyran, thiopyran, morpholine, 1,4-dioxane, piperazine, pyrazine, triazine, 4,5-dihydro-1H-imidazole, or 1,3-dioxolane.

20 23. The use according to claim 1, wherein



24. The use according to claim 1, wherein in formula II,

each R^j is independently -H, halogen, -OH, -NH₂, -CN, =O, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkyl substituted by any number of halogen, -(C₁-C₆)alkoxy substituted by any number of halogen, oxazolyl, thiazolyl, or triazolyl;

the ring B is (C₃-C₈)cycloalkyl, 3-14 membered heterocyclyl containing 1-4 heteroatoms independently selected from O, N and S, C₆-C₁₄ aryl, 5-14 membered heteroaryl containing 1-4 heteroatoms independently selected from O, N and S, or 7-14 membered bicyclic or tricyclic fused ring group containing 0-4 heteroatoms independently selected from O, N and S.

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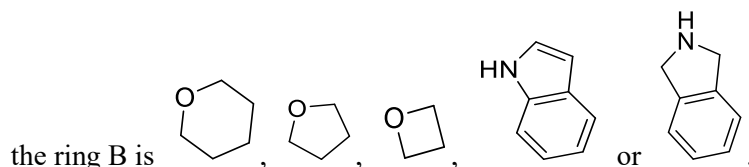
25. The use according to claim 24, wherein in formula II,

the ring B is 3-7 membered oxacycloalkyl or 8-10 membered azabicyclic fused heteroaryl.

26. The use according to claim 25, wherein in formula II,

10 the ring B is oxacycloheptane, oxacyclohexane, tetrahydrofuran, oxetane, oxacyclopropane, 1H-indole or isoindoline.

27. The use according to claim 26, wherein in formula II,

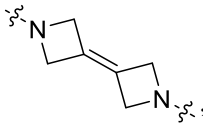


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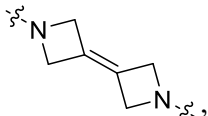
28. The use according to any one of claims 1-27, wherein

any one or more H in the compound of formula I or II are substituted by D.

29. The use according to claim 28, wherein

20 in the compound of formula I or II, any one or more H in the structure “” are substituted by D, or any one or more H in R⁴ are substituted by D.

30. The use according to claim 29, wherein

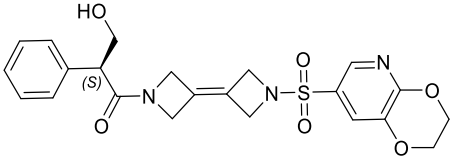
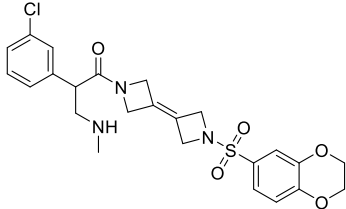
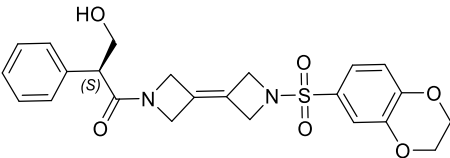
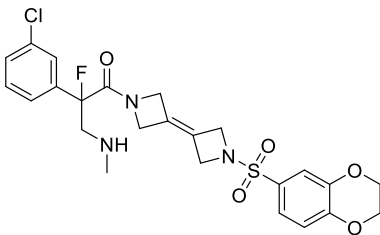
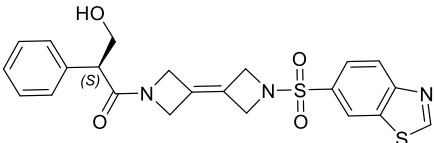
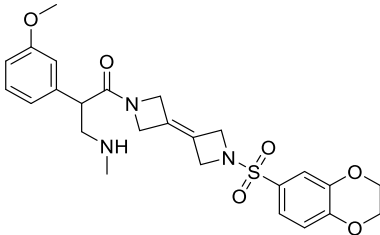
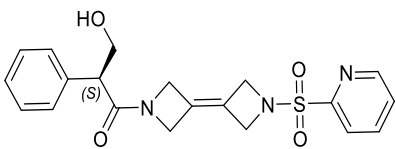
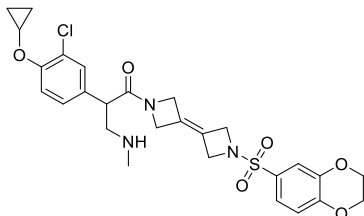
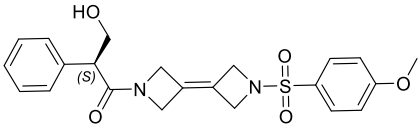
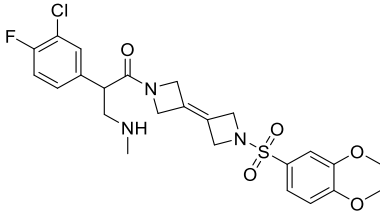
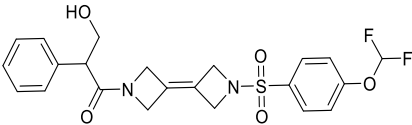
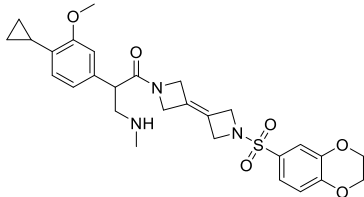
in the compound of formula I or II, all H in the structure “” are substituted by D.

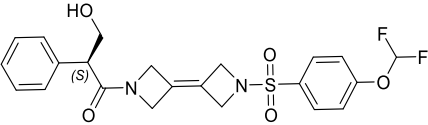
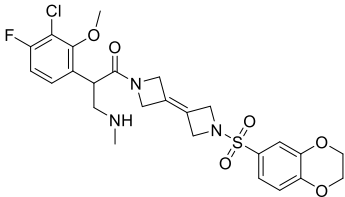
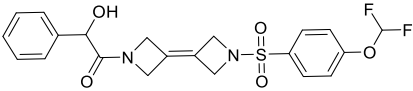
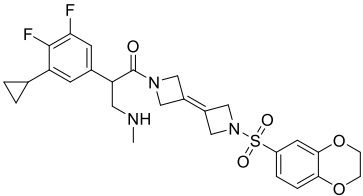
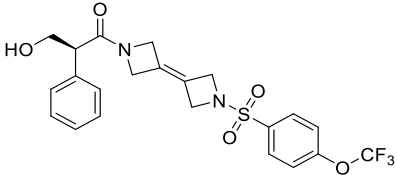
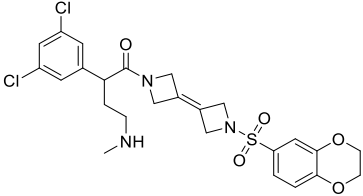
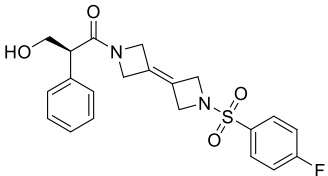
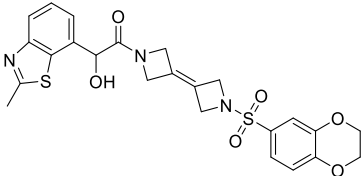
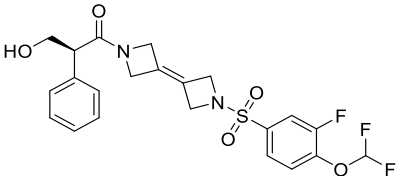
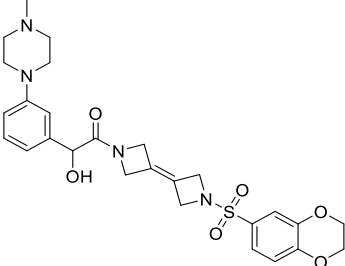
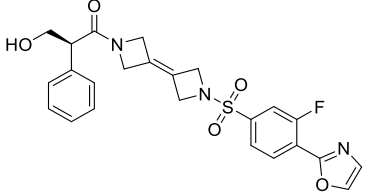
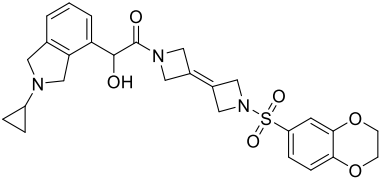
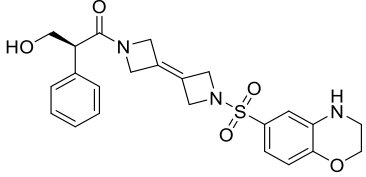
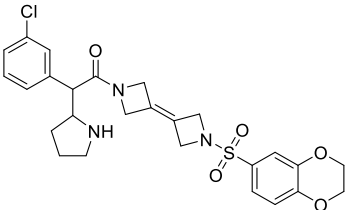
25

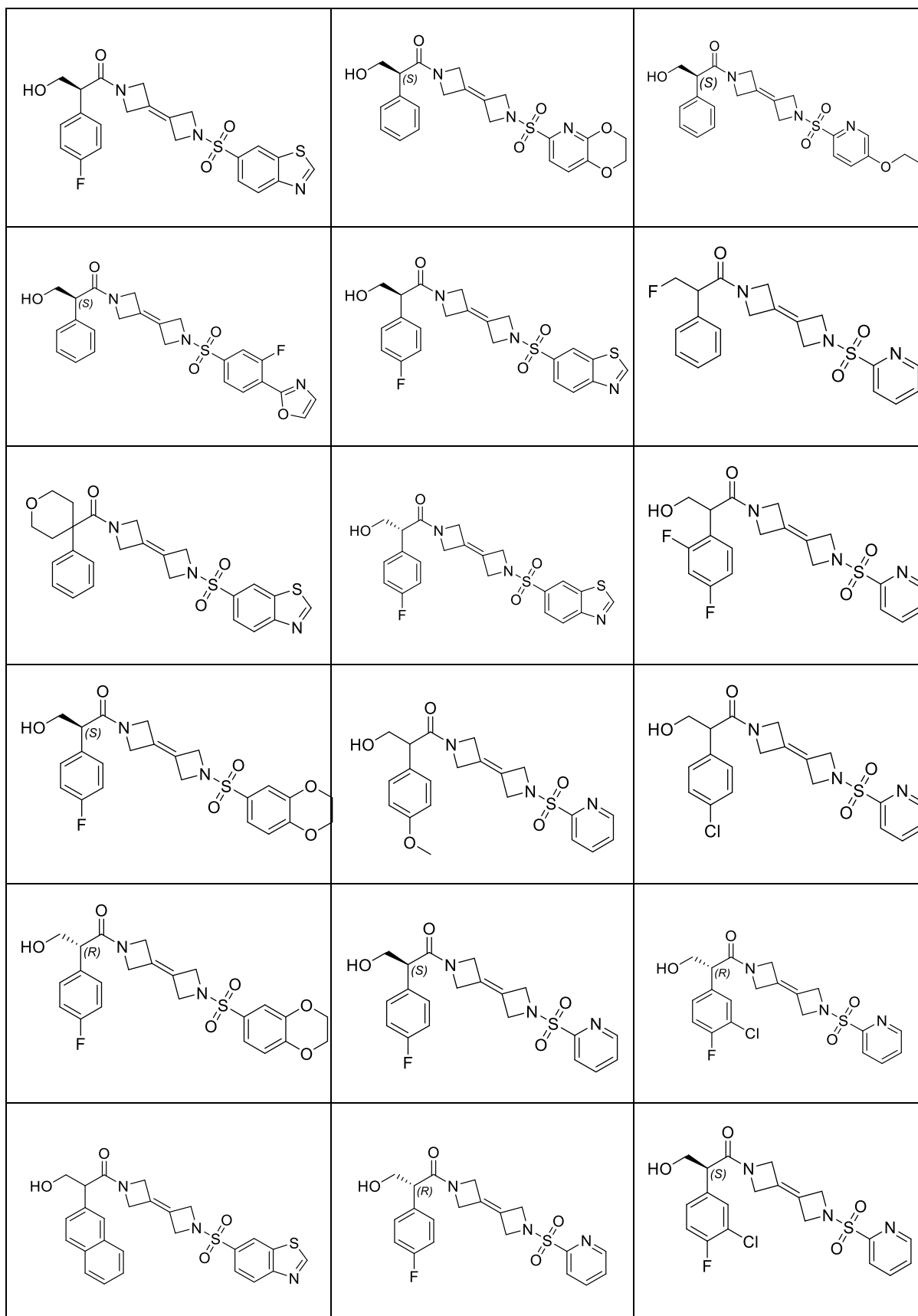
31. The use according to claim 28, wherein

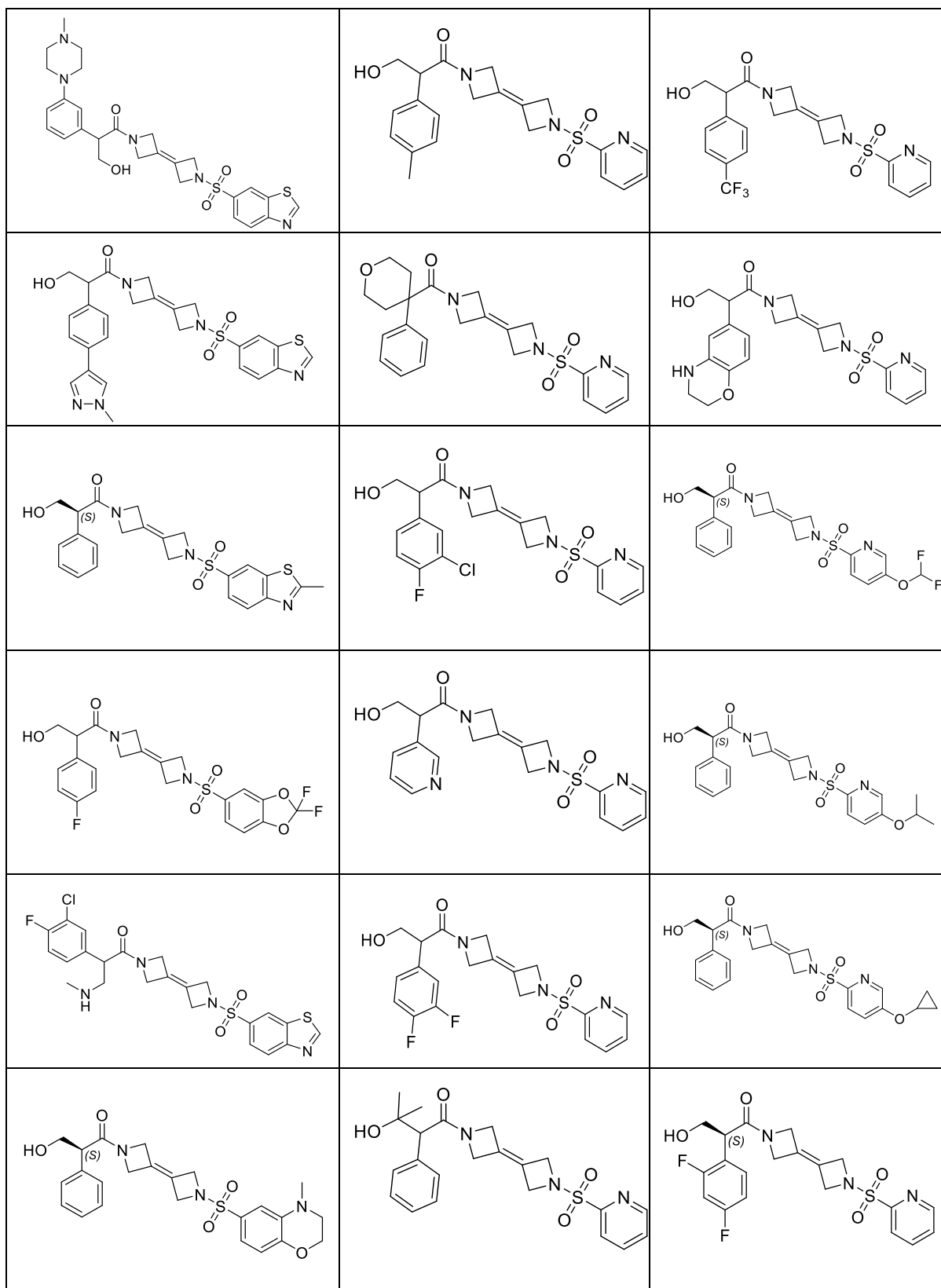
R^1 , R^2 or R^3 is independently and optionally substituted by D when being selected as H.

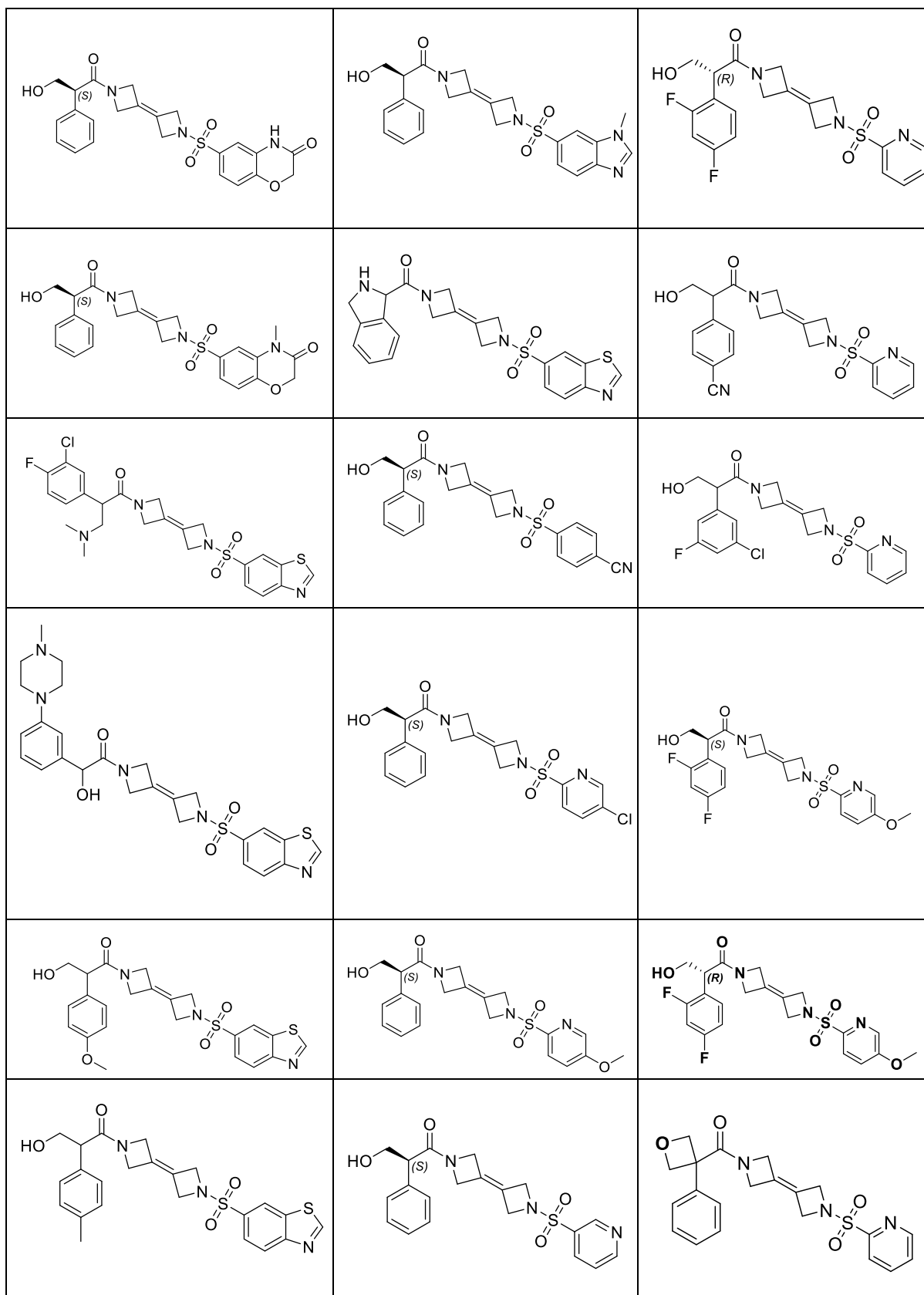
32. The use according to claim 1, wherein the compound is selected from:

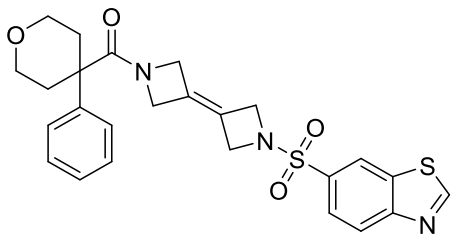
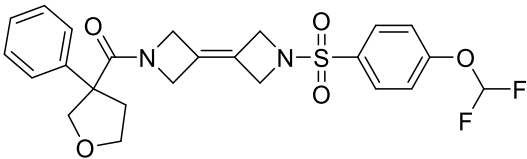
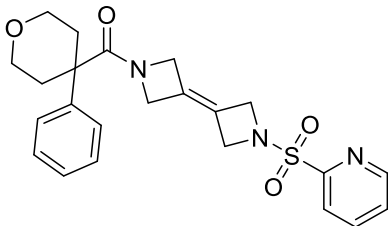
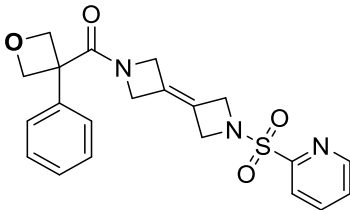
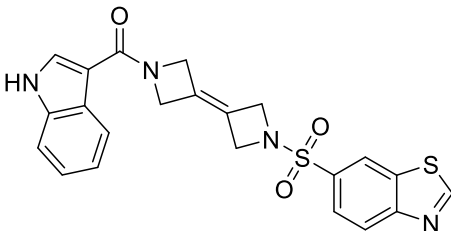
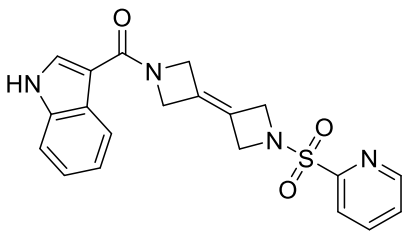
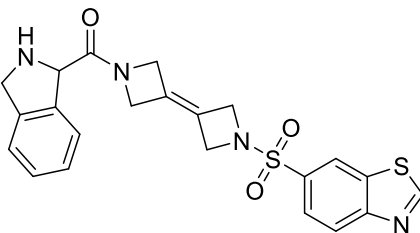
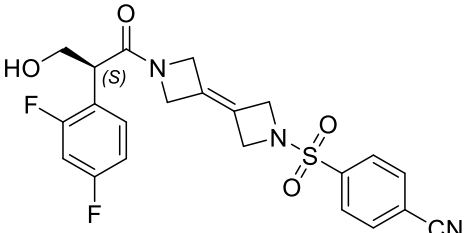
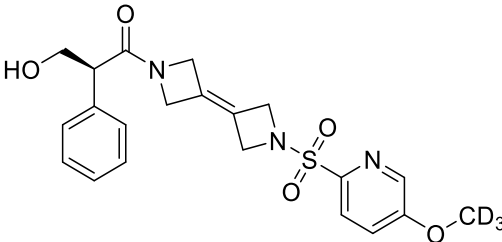
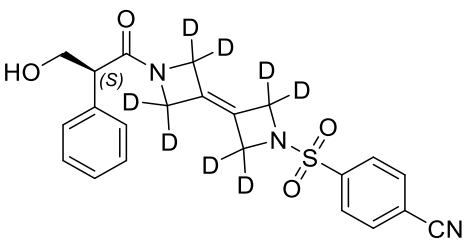
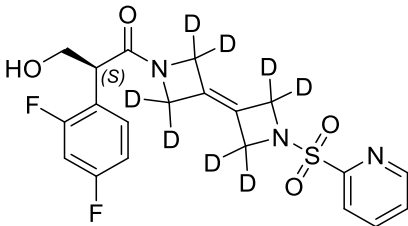
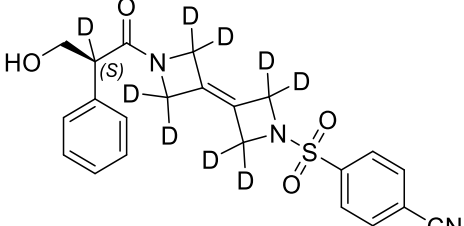
	
	
	
	
	
	







33. The use according to any one of claims 1-32, wherein the pharmaceutical composition is presented in a dosage form of tablet, capsule, granule, pill, paste, powder, tincture, film, patch, liniment, implant, injection, lozenge, drop, spray, aerosol, nebulized inhaler, gel, suppository or ointment.

5 34. The use according to any one of claims 1-32, wherein the pharmaceutical composition is administered in an administration route of oral, intravenous, rectal, parenteral, topical, transdermal, ocular, nasal, buccal or pulmonary (inhalation).

10 35. The use according to claim 34, wherein the pharmaceutical composition is administered in the oral administration route.

15 36. A method for treating or preventing anemia-related disease, comprising administering an active ingredient of 0.05 mg to 1000 mg, the active ingredient is the active ingredient of the use according to any one of claims 1-32, and the anemia-related disease is the disease of the use according to any one of claims 1-4.