

FIVE-MEMBERED AND SIX-MEMBERED NITROGEN-CONTAINING COMPOUND, AND INTERMEDIATE, PREPARATION METHOD AND USE THEREOF

The present application claims the priority to Chinese Patent Application No. 2022107849339 filed on June 29, 2022. The present application claims the priority to Chinese Patent Application No. 2022115596106 filed on December 06, 2022. The present application claims the priority to Chinese Patent Application No. 2023107306040 filed on June 19, 2023. The present application makes reference to the full texts of the Chinese Patent Applications above.

FIELD OF THE INTVENTION

The present invention relates to a 5-membered-fused 6-membered nitrogen-containing compound, intermediates thereof, preparation method therefor, and uses thereof.

BACKGROUND OF THE INVENTION

PARG, the first identified poly (ADP-ribose) hydrolase that is encoded by a single gene (Mirella et al. Human poly (ADP-ribose) glycohydrolase is expressed in alternative splice variants yielding isoforms that localize to different cell compartments. Experimental Cell Research, 2004, 297(2):521-532.), can hydrolyze the O-glycosidic bonds between ADP-ribose subunits. PARG consists of four domains (Meyer B et al. Clustered DNA damage induces pan-nuclear H2AX phosphorylation mediated by ATM and DNA-PK. Nucleic Acids Res, 2003, 41:6109-6118.; O'Sullivan J. et al. Emerging roles of eraser enzymes in the dynamic control of protein ADP-ribosylation. Nature Communication, 2019, 10,1182.), including an N-terminus disordered domain, a linker domain, a C-terminus catalytic domain, and an ADP-ribose binding domain. The non-conserved N-terminus disordered domain is not essential for in vitro activity, and the C-terminus ADP-ribose binding domain is highly conserved with other macro-domains and forms, together with the catalytic domain, the smallest structure with intact enzymatic activity in vitro (Slade D et al. The structure and catalytic mechanism of a poly (ADP-ribose) glycohydrolase. Nature, 2011, 477:616-620.).

Poly ADP-ribosylation (PARylation) is a unique post-translational modification, which is crucial for maintaining the genome stability in different signaling pathways, in particular in DNA damage repair. Poly ADP-ribose, PAR for short, consists of adenosine diphosphate-ribose units. It is formed with NAD⁺ as a donor under the catalysis of poly ADP-ribose polymerases (PARPs), and can be rapidly degraded by polyribosyl hydrolases. After DNA damage, many DNA damage response factors recognize PARylation and are recruited by PARylation to places near the site of DNA damage. However, the PARylation needs to be digested timely, such that the DNA damage response factors can directly recognize DNA damage and fulfill their repair functions. Or else, DNA repair factors are trapped near the site of DNA damage by PARylation

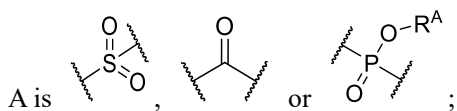
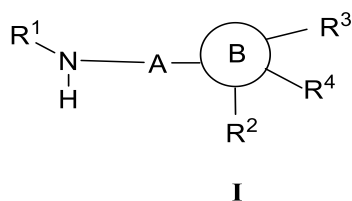
and cannot perform repair properly. Therefore, inhibiting the dePARylation, which is the direct downstream step of PARylation in DNA repair, would affect the PARylation-dependent DNA damage repair and selectively kill tumor cells with DNA repair deficiency.

PARG, as the most important poly (ADP-ribose) hydrolase, exerts its function in about 90% of intracellular PAR (Laetitia D et al. Poly (ADP-ribose) glycohydrolase (PARG) and its therapeutic potential. *Front Biosci*, 2009, 14(5): 1619-1626.), as well as in many cellular processes such as DNA damage repair, DNA replication, chromatin regulation, transcription and apoptosis. Its dysfunction leads to the imbalance of intracellular PAR level and thus affect the transformation and invasion of cancer cells (Rack J D et al. Macrodomain: structure, function, evolution, and catalytic activities. *Annu Rev Biochem*. 2016, 85:431-454; Marques M et al. Oncogenic activity of poly (ADP-ribose) glycohydrolase. *Oncogene*, 2019, 38:2177-2191). PARG has been shown to be associated with a variety of diseases, and there are data suggesting that (Maud M et al, Oncogenic activity of poly (ADP-ribose) glycohydrolase. *Oncogene*, 2019, 38:2177-2191.) the elevated PARG is associated with poor prognosis of HER2+ patients, and PARG and HER2 synergistically promote the growth of breast cancer cells, and inhibiting the PARG significantly affects the growth and migration of breast cancer. In addition, studies have shown that (Mincheng Y et al. PARG inhibition limits HCC progression and potentiates the efficacy of immune checkpoint therapy. *Hepatic and Biliary Cancer*, 2022, S0168-8278(22)00072-1.) high expression of PARG is closely related to poor prognosis of liver cancer, and hepatocyte-specific PARG function loss affects oncogenesis. Hence, PARG inhibitors have attracted more and more attention as potential therapeutic means. At present, there are a variety of PARG inhibitors under development, which are all in the preclinical research stage. Therefore, it is of great research significance to develop small molecule medicaments capable of targeting and inhibiting PARG activity to provide patients with safer and more effective PARG inhibitors.

SUMMARY OF THE INVENTION

The technical problem to be solved by the present invention is to overcome the defect of relatively unitary structure of PARG inhibitor compounds in the prior art, and to this end, the present invention provides a 5-membered-fused 6-membered nitrogen-containing compound, intermediates thereof, a preparation method therefor, and uses thereof. The compound of the present invention has a better PARG inhibitory activity. In addition, the compound of the present invention is greatly improved in permeability and/or solubility compared with the existing inventions.

The present invention provides a compound of formula I, a pharmaceutically acceptable salt thereof or an isotopic compound thereof;



R^A is hydrogen or C_1 - C_6 alkyl;

ring B is a 5-membered-fused 6-membered heteroaromatic ring unsubstituted or substituted by one or two R^B or a 5-membered-fused 5-membered heteroaromatic ring unsubstituted or substituted by one or two R^B ; the heteroatom in the 5-membered-fused 6-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-membered-fused 5-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^B is each independently selected from oxo, hydroxyl, halogen or C_1 - C_6 alkyl, or two R^B , together with the atom to which they are attached, form 3-6 membered cycloalkyl;

R^1 is hydroxyl, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1} , C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or

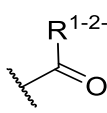
more R^{1-3} , or amino unsubstituted or substituted by one or two R^{1-5} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

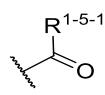
R^{1-1} is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-1-1} , C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1-2} or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-1-3} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^{1-1-1} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-2} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-3} is each independently selected from deuterium, hydroxyl, cyano or halogen;

R^{1-2} is each independently selected from deuterium, hydroxyl, cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} , C_2 - C_6 alkynyl unsubstituted or substituted by one or more R^{1-2-2} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-2-3} , C_2 - C_6 alkenyl unsubstituted or substituted by one

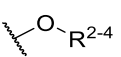
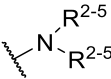
or more R^{1-2-4} , amino unsubstituted or substituted by one or two R^{1-2-5} or ; R^{1-2-1} is each

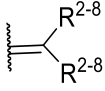
independently selected from deuterium, halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻¹⁻¹; R¹⁻²⁻¹⁻¹ is each independently halogen; R¹⁻²⁻² is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻²⁻¹; R¹⁻²⁻²⁻¹ is each independently halogen; R¹⁻²⁻³ is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻³⁻¹; R¹⁻²⁻³⁻¹ is each independently halogen; R¹⁻²⁻⁴ is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻⁴⁻¹; R¹⁻²⁻⁴⁻¹ is each independently halogen; R¹⁻²⁻⁶ is each independently amino; R¹⁻²⁻⁵ is each

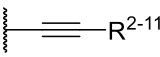
independently ; R¹⁻²⁻⁵⁻¹ is each independently C₁-C₆ alkyl; R¹⁻³ is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹, C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻³⁻² or C₂-C₆ alkynyl; R¹⁻³⁻¹ is each independently halogen; R¹⁻³⁻² is each independently halogen; R¹⁻⁴ is C₁-C₆ alkyl;

R¹⁻⁵ is each independently selected from C₁-C₆ alkyl,  or C₃-C₆ cycloalkyl; R¹⁻⁵⁻¹ is C₁-C₆ alkyl or amino;

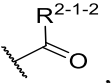
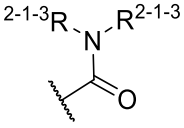
or, the atom in R¹ is attached to the atom in A to form 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁰; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R⁰ is each independently selected from C₁-C₆ alkyl or oxo;

R² is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R²⁻¹, 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻², 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³, , , C₁-C₆ alkyl unsubstituted or substituted by one

or more R²⁻⁶, , , C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻⁹, C₃-C₆

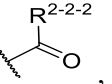
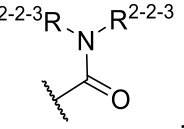
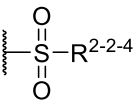
cycloalkenyl unsubstituted or substituted by one or more R²⁻¹⁰, or ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻¹ is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or

more R^{2-1-1} , , ,  or C₁-C₆ alkoxy unsubstituted or substituted by one or more R^{2-1-4} ;

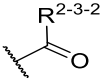
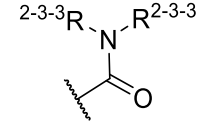
R^{2-1-1} is each independently selected from cyano or halogen; R^{2-1-2} is hydrogen or C₁-C₆ alkyl; R^{2-1-3} is each independently selected from hydrogen or C₁-C₆ alkyl; R^{2-1-4} is each independently halogen;

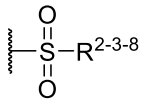
R^{2-2} is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or

more R^{2-2-1} , , , , C₁-C₆ alkoxy or  ;

R^{2-2-1} is each independently selected from cyano or halogen; R^{2-2-2} is hydrogen or C₁-C₆ alkyl; R^{2-2-3} is each independently selected from hydrogen or C₁-C₆ alkyl; R^{2-2-4} is each independently selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

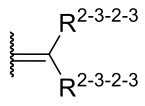
R^{2-3} is each independently selected from cyano, oxo, hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or

substituted by one or more R^{2-3-1} , , , , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3-4} , C₁-C₆ alkoxy unsubstituted or substituted by one or more R^{2-3-5} , C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R^{2-3-6} , amino unsubstituted or substituted

by one or more R^{2-3-7} , , or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-3-9} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-1} is each independently selected from hydroxyl, cyano, halogen, C₁-C₆ alkoxy unsubstituted or substituted by one or more $R^{2-3-1-1}$, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more $R^{2-3-1-2}$, or amino unsubstituted or substituted by one or more $R^{2-3-1-3}$;

R^{2-3-2} is hydrogen, C₁-C₆ alkyl unsubstituted or substituted by one or more $R^{2-3-2-1}$, C₃-C₆ cycloalkyl

unsubstituted or substituted by one or more $R^{2-3-2-2}$, , C₁-C₆ alkoxy unsubstituted or substituted by one or more $R^{2-3-2-4}$, 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-5}$, or 5-10 membered heteroaryl unsubstituted or substituted by one or more $R^{2-3-2-6}$; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1,

2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻⁴ is each independently selected from C₁-C₆ alkyl or oxo;

R²⁻³⁻⁵ is each independently selected from halogen or deuterium;

R²⁻³⁻⁶ is each independently C₁-C₆ alkyl;

R²⁻³⁻⁷ is each independently C₁-C₆ alkyl;

R²⁻³⁻⁸ is each independently selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

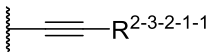
R²⁻³⁻⁹ is each independently C₁-C₆ alkyl;

R²⁻³⁻¹⁻¹ is each independently halogen;

R²⁻³⁻¹⁻² is each independently C₁-C₆ alkoxy;

R²⁻³⁻¹⁻³ is each independently C₁-C₆ alkyl;

R²⁻³⁻²⁻¹ is each independently selected from halogen, carboxyl, hydroxyl, oxo, C₁-C₆ alkoxy,

, amino unsubstituted or substituted by one or more R²⁻³⁻²⁻¹⁻², or 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻³⁻²⁻¹⁻³; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³⁻²⁻¹⁻¹ is each independently selected from C₁-C₆ alkyl or 6-10 membered aryl;

R²⁻³⁻²⁻¹⁻² is each independently C₁-C₆ alkyl;

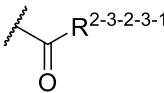
R²⁻³⁻²⁻¹⁻³ is each independently C₁-C₆ alkyl;

R²⁻³⁻²⁻² is each independently selected from halogen, hydroxyl, C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻¹, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻², or amino unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻³;

R²⁻³⁻²⁻²⁻¹ is each independently selected from halogen or hydroxyl;

R²⁻³⁻²⁻²⁻² is each independently selected from carboxyl, halogen, deuterium, oxo or hydroxyl;

R²⁻³⁻²⁻²⁻³ is each independently C₁-C₆ alkyl;

R²⁻³⁻²⁻³ is each independently selected from hydrogen or ; R²⁻³⁻²⁻³⁻¹ is each independently 6-10 membered aryl unsubstituted or substituted by one or more R²⁻³⁻²⁻³⁻¹⁻¹; R²⁻³⁻²⁻³⁻¹⁻¹ is each independently C₁-C₆ alkoxy;

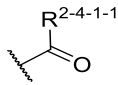
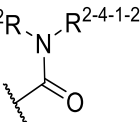
R²⁻³⁻²⁻⁴ is each independently halogen;

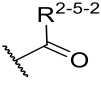
R²⁻³⁻²⁻⁵ is each independently selected from halogen, hydroxyl, oxo, C₁-C₆ alkoxy, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻⁵⁻¹; R²⁻³⁻²⁻⁵⁻¹ is each independently halogen;

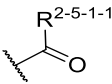
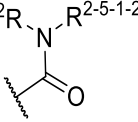
$R^{2-3-2-6}$ is each independently C_1 - C_6 alkyl;

$R^{2-3-3-1}$ is each independently amino unsubstituted or substituted by one or more $R^{2-3-3-1-1}$; $R^{2-3-3-1-1}$ is each independently C_1 - C_6 alkyl;

each R^{2-4} is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} or C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{2-4-4} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-4-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl,  or ; R^{2-4-2} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-4} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; $R^{2-4-1-1}$ is C_1 - C_6 alkyl; $R^{2-4-1-2}$ is C_1 - C_6 alkyl;

R^{2-5} is each independently selected from hydrogen, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-5-1} , , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-5-3} , or C_1 - C_6 alkyl; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

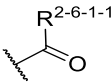
R^{2-5-1} is each independently selected from  or ; $R^{2-5-1-1}$ is hydrogen or C_1 - C_6 alkyl;

$R^{2-5-1-2}$ is each independently selected from hydrogen or C_1 - C_6 alkyl;

R^{2-5-2} is independently C_1 - C_6 alkyl;

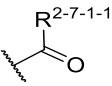
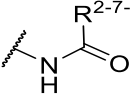
R^{2-5-3} is each independently C_1 - C_6 alkoxy;

R^{2-6} is each independently selected from halogen, C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1 - C_6 alkyl or ; $R^{2-6-1-1}$ is C_1 - C_6 alkyl;

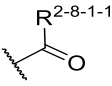
R²⁻⁶⁻² is each independently selected from halogen or C₁-C₆ alkyl;

R²⁻⁷ is C₁-C₆ alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻⁷⁻¹ or 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻⁷⁻²; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻⁷⁻¹ is each independently selected from halogen, C₁-C₆ alkyl,  or ; R²⁻⁷⁻¹⁻¹ is C₁-C₆ alkyl; R²⁻⁷⁻¹⁻² is C₁-C₆ alkyl;

R²⁻⁷⁻² is each independently selected from halogen or C₁-C₆ alkyl;

R²⁻⁸ is each independently C₁-C₆ alkyl, or two R²⁻⁸, together with the atom to which they are attached, form 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻⁸⁻¹; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻⁸⁻¹ is each independently ; R²⁻⁸⁻¹⁻¹ is hydrogen or C₁-C₆ alkyl;

R²⁻⁹ is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻⁹⁻¹; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R²⁻⁹⁻¹ is each independently C₁-C₆ alkyl;

R²⁻¹⁰ is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻¹⁰⁻¹; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R²⁻¹⁰⁻¹ is each independently C₁-C₆ alkyl;

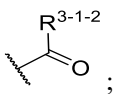
R²⁻¹¹ is each independently selected from 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻¹¹⁻¹, or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻¹¹⁻²; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻¹¹⁻¹ is each independently C₁-C₆ alkyl; R²⁻¹¹⁻² is each independently C₁-C₆ alkyl;

R³ is 5-10 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹ or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R³⁻²; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number

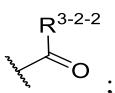
of heteroatom(s) is 1, 2 or 3;

R^{3-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-1-1} or  ;

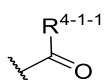
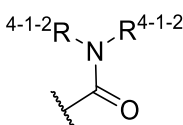
R^{3-1-1} is each independently selected from halogen or hydroxyl; R^{3-1-2} is C_1 - C_6 alkyl or C_2 - C_6 alkenyl;

R^{3-2} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-2-1} or  ;

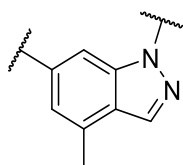
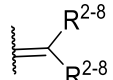
R^{3-2-1} is each independently halogen; R^{3-2-2} is C_1 - C_6 alkyl or C_2 - C_4 alkenyl;

R^4 is hydrogen, deuterium, halogen, cyano, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{4-2} ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

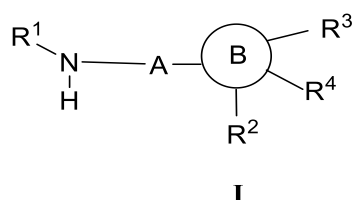
R^{4-1} is each independently  or  ;

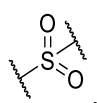
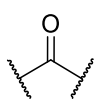
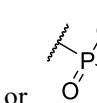
R^{4-2} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{4-2-1} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R^{4-1-1} is C_1 - C_6 alkyl; R^{4-1-2} is each independently C_1 - C_6 alkyl; R^{4-2-1} is each independently C_1 - C_6 alkyl; and

when ring B is  , R^2 is  or  .

The present invention provides a compound of formula I, a pharmaceutically acceptable salt thereof or an isotopic compound thereof;



A is  ,  or  ;

R^A is hydrogen or C_1 - C_6 alkyl;

ring B is a 5-membered-fused 6-membered heteroaromatic ring unsubstituted or substituted by one or two R^B or a 5-membered-fused 5-membered heteroaromatic ring unsubstituted or substituted by one or two R^B ; the heteroatom in the 5-membered-fused 6-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-membered-fused 5-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^B is each independently selected from oxo, hydroxyl, halogen or C_1 - C_6 alkyl, or two R^B , together with the atom to which they are attached, form 3-6 membered cycloalkyl;

R^1 is hydroxyl, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1} , C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or

more R^{1-3} ,  or amino unsubstituted or substituted by one or two R^{1-5} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{1-1} is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-1-1} , C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1-2} or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-1-3} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^{1-1-1} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-2} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-3} is each independently selected from deuterium, hydroxyl, cyano or halogen;

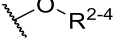
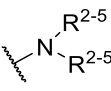
R^{1-2} is each independently selected from deuterium, hydroxyl, cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} , C_2 - C_6 alkynyl unsubstituted or substituted by one or more R^{1-2-2} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-2-3} , C_2 - C_6 alkenyl unsubstituted or substituted by one or more R^{1-2-4} or amino unsubstituted or substituted by one or two R^{1-2-5} ; R^{1-2-1} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-1-1}$; $R^{1-2-1-1}$ is each independently selected from halogen; R^{1-2-2} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-2-1}$; $R^{1-2-2-1}$ is each independently selected from halogen; R^{1-2-3} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-3-1}$; $R^{1-2-3-1}$ is each independently selected from halogen; R^{1-2-4} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-4-1}$; $R^{1-2-4-1}$ is each independently halogen;

R^{1-3} is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-3-2} ; R^{1-3-1} is each independently halogen; R^{1-3-2} is each independently halogen;

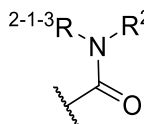
R^{1-4} is C_1 - C_6 alkyl;

R^{1-5} is each independently selected from C_1 - C_6 alkyl,  or C_3 - C_6 cycloalkyl;
 R^{1-5-1} is C_1 - C_6 alkyl or amino;

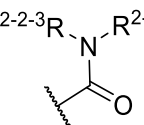
or, the atom in R^1 is attached to the atom in A to form 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from C_1 - C_6 alkyl or oxo;

R^2 is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-2} , 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} , , , C_1 - C_6 alkyl unsubstituted or substituted by one

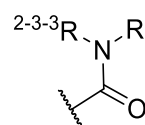
or more R^{2-6} ,  or ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-1} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{2-1-1} , ,  or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{2-1-4} ;

R^{2-1-1} is each independently selected from cyano or halogen; R^{2-1-2} is hydrogen or C_1 - C_6 alkyl; R^{2-1-3} is each independently selected from hydrogen or C_1 - C_6 alkyl; R^{2-1-4} is each independently halogen;

R^{2-2} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{2-2-1} , , or ;

R^{2-2-1} is each independently selected from cyano or halogen; R^{2-2-2} is hydrogen or C_1 - C_6 alkyl; R^{2-2-3} is each independently selected from hydrogen or C_1 - C_6 alkyl;

R^{2-3} is each independently selected from cyano, oxo, hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{2-3-1} , , , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3-4} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more

R²⁻³⁻⁵; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³⁻¹ is each independently selected from cyano, halogen, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹;

R²⁻³⁻² is hydrogen or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻¹;

R²⁻³⁻³ is each independently hydrogen or C₁-C₆ alkyl;

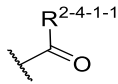
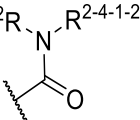
R²⁻³⁻⁴ is each independently C₁-C₆ alkyl;

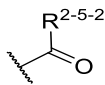
R²⁻³⁻⁵ is each independently halogen;

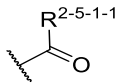
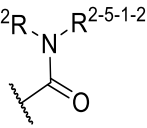
R²⁻³⁻¹⁻¹ is each independently halogen;

R²⁻³⁻²⁻¹ is each independently halogen;

each R²⁻⁴ is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻⁴⁻¹, 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻⁴⁻², 6-10 membered aryl unsubstituted or substituted by one or more R²⁻⁴⁻³ or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻⁴⁻⁴; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻⁴⁻¹ is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl,  or ; R²⁻⁴⁻² is each independently selected from hydroxyl, halogen or C₁-C₆ alkyl; R²⁻⁴⁻³ is each independently selected from hydroxyl, halogen or C₁-C₆ alkyl; R²⁻⁴⁻⁴ is each independently selected from hydroxyl, halogen or C₁-C₆ alkyl; R²⁻⁴⁻¹⁻¹ is C₁-C₆ alkyl; R²⁻⁴⁻¹⁻² is C₁-C₆ alkyl;

R²⁻⁵ is each independently hydrogen, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻⁵⁻¹, or ; the heteroatom in the 4-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

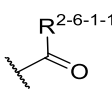
R²⁻⁵⁻¹ is each independently selected from  or ; R²⁻⁵⁻¹⁻¹ is hydrogen or C₁-C₆ alkyl;

R²⁻⁵⁻¹⁻² is each independently selected from hydrogen or C₁-C₆ alkyl;

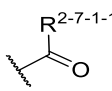
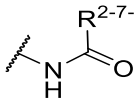
R²⁻⁵⁻² is independently C₁-C₆ alkyl;

R²⁻⁶ is each independently selected from halogen, C₁-C₆ alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻⁶⁻¹ or 5-10 membered heteroaryl unsubstituted or substituted

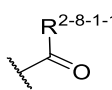
by one or more R^{2-6-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1 - C_6 alkyl or ; $R^{2-6-1-1}$ is C_1 - C_6 alkyl;
 R^{2-6-2} is each independently selected from halogen or C_1 - C_6 alkyl;

R^{2-7} is C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

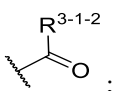
R^{2-7-1} is each independently selected from halogen, C_1 - C_6 alkyl,  or ; $R^{2-7-1-1}$ is C_1 - C_6 alkyl;
 R^{2-7-2} is each independently selected from halogen or C_1 - C_6 alkyl;

R^{2-8} is each independently C_1 - C_6 alkyl, or two R^{2-8} , together with the atom to which they are attached, form 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-8-1} is each independently ; $R^{2-8-1-1}$ is hydrogen or C_1 - C_6 alkyl;

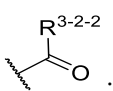
R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{3-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-1-1} or ;

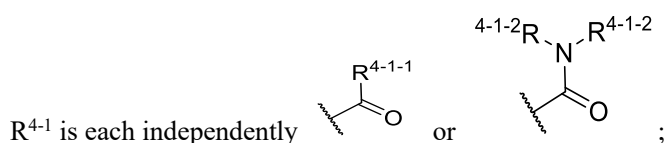
R^{3-1-1} is each independently halogen; R^{3-1-2} is C_1 - C_6 alkyl or C_2 - C_6 alkenyl;

R^{3-2} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-2-1} or ;

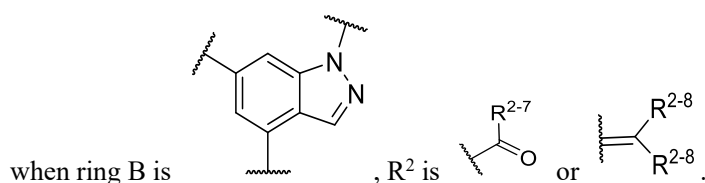
R^{3-2-1} is each independently halogen; R^{3-2-2} is C_1 - C_6 alkyl or C_2 - C_4 alkenyl;

R⁴ is hydrogen, halogen, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁴⁻¹ or C₁-C₆ alkyl unsubstituted or substituted by one or more R⁴⁻²; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;



R⁴⁻² is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R⁴⁻²⁻¹; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R⁴⁻¹⁻¹ is C₁-C₆ alkyl; R⁴⁻¹⁻² is each independently C₁-C₆ alkyl; R⁴⁻²⁻¹ is each independently C₁-C₆ alkyl; and



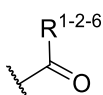
In a preferred embodiment, in the compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof, some groups can be defined as follows, and other groups can be defined as in any one of the above embodiments (hereinafter referred to as “in a preferred embodiment”).

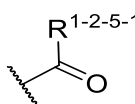
In a preferred embodiment, R¹ is hydroxyl, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻², 3-6 membered heterocycloalkyl

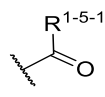
unsubstituted or substituted by one or more R¹⁻³,  or amino unsubstituted or substituted by one or two R¹⁻⁵; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻¹⁻¹, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹⁻² or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻¹⁻³; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R¹⁻¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻² is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻³ is each independently selected from deuterium, hydroxyl, cyano or halogen;

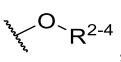
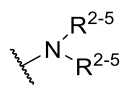
R¹⁻² is each independently selected from deuterium, hydroxyl, halogen, C₂-C₆ alkynyl unsubstituted or substituted by one or more R¹⁻²⁻², C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻³, C₂-C₆ alkenyl unsubstituted or substituted by one or more R¹⁻²⁻⁴, amino unsubstituted or substituted by one or two

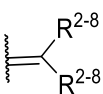
R^{1-2-5} or ; $R^{1-2-2-1}$ is each independently halogen; R^{1-2-3} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-3-1}$; $R^{1-2-3-1}$ is each independently halogen; R^{1-2-4} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-4-1}$; $R^{1-2-4-1}$ is each independently halogen; R^{1-2-6} is each

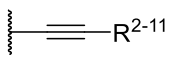
independently amino; R^{1-2-5} is each independently ; $R^{1-2-5-1}$ is each independently C_1 - C_6 alkyl; R^{1-3} is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-3-2} or C_2 - C_6 alkynyl; R^{1-3-1} is each independently halogen; R^{1-3-2} is each independently halogen; R^{1-4} is C_1 - C_6 alkyl;

R^{1-5} is each independently selected from C_1 - C_6 alkyl,  or C_3 - C_6 cycloalkyl; R^{1-5-1} is C_1 - C_6 alkyl or amino;

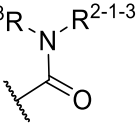
or, the atom in R^1 is attached to the atom in A to form 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from C_1 - C_6 alkyl or oxo.

In a preferred embodiment, R^2 is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-2} , 4-12 membered heterocycloalkyl substituted by one or more R^{2-3} , , , C_1 - C_6 alkyl unsubstituted or

substituted by one or more R^{2-6} , , , C_3 - C_6 cycloalkyl unsubstituted or substituted by one or

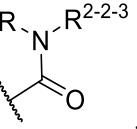
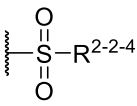
more R^{2-9} , C_3 - C_6 cycloalkenyl unsubstituted or substituted by one or more R^{2-10} , or ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-1} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

more R^{2-1-1} , ,  or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{2-1-4} ;

R^{2-1-1} is each independently selected from cyano or halogen; R^{2-1-2} is hydrogen or C_1 - C_6 alkyl; R^{2-1-3} is each independently selected from hydrogen or C_1 - C_6 alkyl; R^{2-1-4} is each independently halogen;

R^{2-2} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

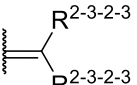
more R^{2-2-1} , , , C_1 - C_6 alkoxy or  ;

R^{2-2-1} is each independently selected from cyano or halogen; R^{2-2-2} is hydrogen or C_1 - C_6 alkyl; R^{2-2-3} is each independently selected from hydrogen or C_1 - C_6 alkyl; R^{2-2-4} is each independently selected from C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl;

R^{2-3} is each independently selected from C_1 - C_6 alkyl substituted by one or more R^{2-3-1} , , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3-4} , amino unsubstituted or substituted by one or more R^{2-3-7} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-3-9} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-1} is each independently selected from cyano, or C_3 - C_6 cyano unsubstituted or substituted by one or more $R^{2-3-1-2}$;

R^{2-3-2} is hydrogen, or C_1 - C_6 alkyl substituted by one or more $R^{2-3-2-1}$, C_3 - C_6 cycloalkyl substituted by one or

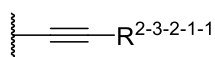
more $R^{2-3-2-2}$, , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-5}$, 5-10 membered heteroaryl unsubstituted or substituted by one or more $R^{2-3-2-6}$; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-4} is each independently C_1 - C_6 alkyl;

R^{2-3-7} is each independently C_1 - C_6 alkyl;

R^{2-3} is each independently selected from oxo or C_1 - C_6 alkyl;

$R^{2-3-1-2}$ is each independently C_1 - C_6 alkoxy; $R^{2-3-2-1}$ is each independently selected from hydroxyl, oxo,



, or 5-10 membered heteroaryl unsubstituted or substituted by one or more $\text{R}^{2-3-2-1-3}$; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

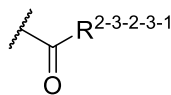
$\text{R}^{2-3-2-1-1}$ is each independently selected from $\text{C}_1\text{-C}_6$ alkyl or 6-10 membered aryl; $\text{R}^{2-3-2-1-2}$ is each independently $\text{C}_1\text{-C}_6$ alkyl; $\text{R}^{2-3-2-1-3}$ is each independently $\text{C}_1\text{-C}_6$ alkyl;

$\text{R}^{2-3-2-2}$ is each independently selected from halogen, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl unsubstituted or substituted by one or more $\text{R}^{2-3-2-2-1}$, $\text{C}_1\text{-C}_6$ alkoxy unsubstituted or substituted by one or more $\text{R}^{2-3-2-2-2}$, or amino unsubstituted or substituted by one or more $\text{R}^{2-3-2-2-3}$;

$\text{R}^{2-3-2-2-1}$ is each independently selected from halogen or hydroxyl;

$\text{R}^{2-3-2-2-2}$ is each independently selected from halogen, deuterium, oxo or hydroxyl;

$\text{R}^{2-3-2-2-3}$ is each independently $\text{C}_1\text{-C}_6$ alkyl;

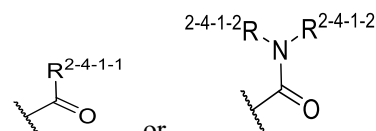


$\text{R}^{2-3-2-3}$ is each independently selected from hydrogen or $\text{---}\text{C}(=\text{O})\text{---}$; $\text{R}^{2-3-2-3-1}$ is each independently 6-10 membered aryl unsubstituted or substituted by one or more $\text{R}^{2-3-2-3-1-1}$; $\text{R}^{2-3-2-3-1-1}$ is each independently $\text{C}_1\text{-C}_6$ alkoxy;

$\text{R}^{2-3-2-4}$ is each independently halogen;

$\text{R}^{2-3-2-5}$ is each independently selected from halogen, hydroxyl, oxo, $\text{C}_1\text{-C}_6$ alkoxy, or $\text{C}_1\text{-C}_6$ alkyl substituted by one or more $\text{R}^{2-3-2-5-1}$; $\text{R}^{2-3-2-5-1}$ is each independently halogen;

$\text{R}^{2-3-2-6}$ is each independently $\text{C}_1\text{-C}_6$ alkyl; R^{2-4} is 4-10 membered heterocycloalkyl substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , or 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

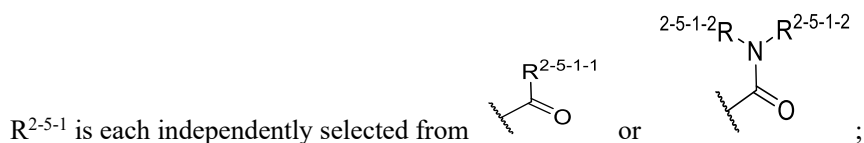


R^{2-4-1} is each independently selected from hydroxyl, halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{---}\text{C}(=\text{O})\text{---R}^{2-4-1-1}$ or $\text{---}\text{C}(=\text{O})\text{---N(R}^{2-4-1-2}\text{)(R}^{2-4-1-2}\text{)---}$; R^{2-4-2} is each independently selected from hydroxyl, halogen or $\text{C}_1\text{-C}_6$ alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or $\text{C}_1\text{-C}_6$ alkyl;

R^{2-5} is each independently selected from hydrogen, 4-10 membered heterocycloalkyl substituted by one or

more R^{2-5-1} , $\text{---}\text{C}(=\text{O})\text{---R}^{2-5-2}$, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-5-3} , or $\text{C}_1\text{-C}_6$ alkyl; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and

the number of heteroatom(s) is 1, 2 or 3;



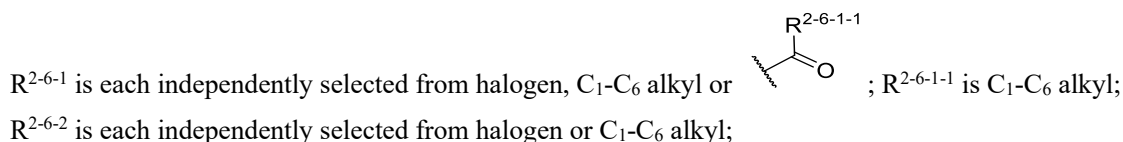
$R^{2-5-1-1}$ is hydrogen or C₁-C₆ alkyl;

$R^{2-5-1-2}$ is each independently selected from hydrogen or C₁-C₆ alkyl;

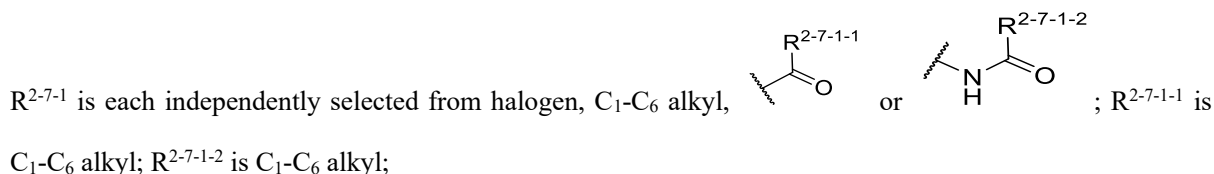
R^{2-5-2} is independently C₁-C₆ alkyl;

R^{2-5-3} is each independently C₁-C₆ alkoxy;

R^{2-6} is each independently selected from halogen, C₁-C₆ alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

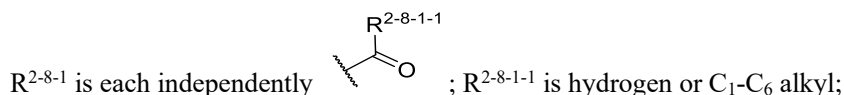


R^{2-7} is C₁-C₆ alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;



R^{2-7-2} is each independently selected from halogen or C₁-C₆ alkyl;

R^{2-8} is each independently C₁-C₆ alkyl, or two R^{2-8} , together with the atom to which they are attached, form 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;



R^{2-9} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-9-1} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R²⁻⁹⁻¹ is each independently C₁-C₆ alkyl;

R²⁻¹⁰ is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻¹⁰⁻¹; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

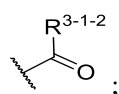
R²⁻¹⁰⁻¹ is each independently C₁-C₆ alkyl;

R²⁻¹¹ is each independently selected from 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻¹¹⁻¹, or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻¹¹⁻²; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻¹¹⁻¹ is each independently C₁-C₆ alkyl; R²⁻¹¹⁻² is each independently C₁-C₆ alkyl.

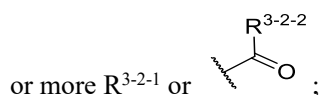
In a preferred embodiment, R³ is 5-10 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹ or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R³⁻²; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R³⁻¹ is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹ or



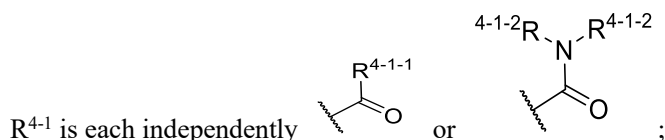
R³⁻¹⁻¹ is each independently selected from hydroxyl; R³⁻¹⁻² is C₁-C₆ alkyl or C₂-C₆ alkenyl;

R³⁻² is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or substituted by one



R³⁻²⁻¹ is each independently halogen; and R³⁻²⁻² is C₁-C₆ alkyl or C₂-C₄ alkenyl.

In a preferred embodiment, R⁴ is deuterium, cyano, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁴⁻¹ or C₁-C₆ alkyl substituted by one or more R⁴⁻²; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;



R⁴⁻² is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R⁴⁻²⁻¹; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R⁴⁻¹⁻¹ is C₁-C₆ alkyl; R⁴⁻¹⁻² is each independently C₁-C₆ alkyl; R⁴⁻²⁻¹ is each independently C₁-C₆ alkyl.

In a preferred embodiment, R^1 is hydroxyl, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1} , C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} , 3-6 membered heterocycloalkyl

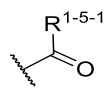
unsubstituted or substituted by one or more R^{1-3} ,  or amino unsubstituted or substituted by one or two R^{1-5} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{1-1} is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-1-1} , C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1-2} or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-1-3} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^{1-1-1} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-2} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-3} is each independently selected from deuterium, hydroxyl, cyano or halogen;

R^{1-2} is each independently selected from deuterium, hydroxyl, halogen, C_2 - C_6 alkynyl unsubstituted or substituted by one or more R^{1-2-2} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-2-3} , C_2 - C_6 alkenyl unsubstituted or substituted by one or more R^{1-2-4} or amino unsubstituted or substituted by one or two R^{1-2-5} ; R^{1-2-2} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-2-1}$; $R^{1-2-2-1}$ is each independently halogen; R^{1-2-3} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-3-1}$; $R^{1-2-3-1}$ is each independently halogen; R^{1-2-4} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-4-1}$; $R^{1-2-4-1}$ is each independently halogen;

R^{1-3} is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-3-2} ; R^{1-3-1} is each independently halogen; R^{1-3-2} is each independently halogen;

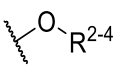
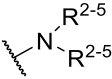
R^{1-4} is C_1 - C_6 alkyl;

R^{1-5} is each independently selected from C_1 - C_6 alkyl,  or C_3 - C_6 cycloalkyl;

R^{1-5-1} is C_1 - C_6 alkyl or amino;

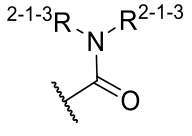
or, the atom in R^1 is attached to the atom in A to form 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from C_1 - C_6 alkyl or oxo.

In a preferred embodiment, R^2 is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-2} , 4-10 membered

heterocycloalkyl substituted by one or more R^{2-3} , , , C_1 - C_6 alkyl unsubstituted or

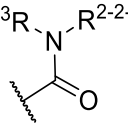
substituted by one or more R^{2-6} ,  or ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-1} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

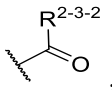
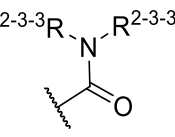
more R^{2-1-1} , ,  or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{2-1-4} ;

R^{2-1-1} is each independently selected from cyano or halogen; R^{2-1-2} is hydrogen or C_1 - C_6 alkyl; R^{2-1-3} is each independently selected from hydrogen or C_1 - C_6 alkyl; R^{2-1-4} is each independently halogen;

R^{2-2} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

more R^{2-2-1} ,  or ;

R^{2-2-1} is each independently selected from cyano or halogen; R^{2-2-2} is hydrogen or C_1 - C_6 alkyl; R^{2-2-3} is each independently selected from hydrogen or C_1 - C_6 alkyl;

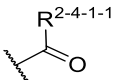
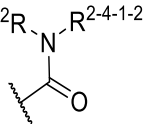
R^{2-3} is each independently selected from C_1 - C_6 alkyl substituted by one or more R^{2-3-1} , , , or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3-4} ; the

heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

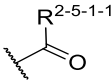
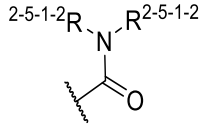
R^{2-3-1} is each independently cyano;

R^{2-3-2} is hydrogen; R^{2-3-4} is each independently C_1 - C_6 alkyl;

R^{2-4} is 4-10 membered heterocycloalkyl substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-4-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl,  or  ;
 R^{2-4-2} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl;

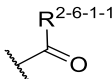
R^{2-5} is each independently hydrogen, 4-10 membered heterocycloalkyl substituted by one or more R^{2-5-1} , or  ; the heteroatom in the 4-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-5-1} is each independently selected from  or  ;
 $R^{2-5-1-1}$ is hydrogen or C_1 - C_6 alkyl;

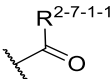
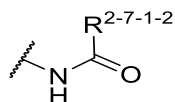
$R^{2-5-1-2}$ is each independently selected from hydrogen or C_1 - C_6 alkyl;

R^{2-5-2} is independently C_1 - C_6 alkyl;

R^{2-6} is each independently selected from halogen, C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1 - C_6 alkyl or  ; $R^{2-6-1-1}$ is C_1 - C_6 alkyl;
 R^{2-6-2} is each independently selected from halogen or C_1 - C_6 alkyl;

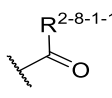
R^{2-7} is C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-7-1} is each independently selected from halogen, C_1 - C_6 alkyl,  or  ; $R^{2-7-1-1}$ is C_1 - C_6 alkyl; $R^{2-7-1-2}$ is C_1 - C_6 alkyl;

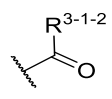
R^{2-7-2} is each independently selected from halogen or C_1 - C_6 alkyl;

R^{2-8} is each independently C_1 - C_6 alkyl, or two R^{2-8} , together with the atom to which they are attached, form 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in the

4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

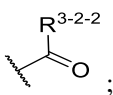
R^{2-8-1} is each independently ; and $R^{2-8-1-1}$ is hydrogen or C₁-C₆ alkyl.

In a preferred embodiment, R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{3-1} is each independently selected from hydroxyl, halogen or ;

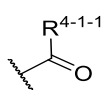
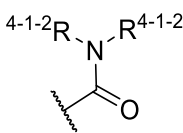
R^{3-1-2} is C₁-C₆ alkyl or C₂-C₆ alkenyl;

R^{3-2} is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or substituted by one

or more R^{3-2-1} or ;

R^{3-2-1} is each independently halogen; and R^{3-2-2} is C₁-C₆ alkyl or C₂-C₄ alkenyl.

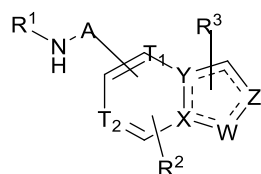
In a preferred embodiment, R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} or C₁-C₆ alkyl unsubstituted or substituted by one or more R^{4-2} ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{4-1} is each independently  or ;

R^{4-2} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{4-2-1} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

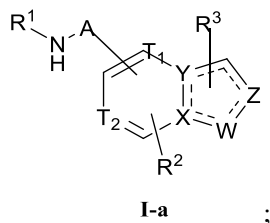
R^{4-1-1} is C₁-C₆ alkyl; R^{4-1-2} is each independently C₁-C₆ alkyl; R^{4-2-1} is each independently C₁-C₆ alkyl.

In a preferred embodiment, in the compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof, some groups can be defined as follows, and other groups can be defined as in any of the above embodiments (hereinafter referred to as “in a preferred embodiment”):



I-a

, wherein the compound of formula I is a compound of formula I-a,



Y is C or N, X is C or N,

W is N, CH, O, NR⁴ or CR⁴;

Z is CH, O or N;

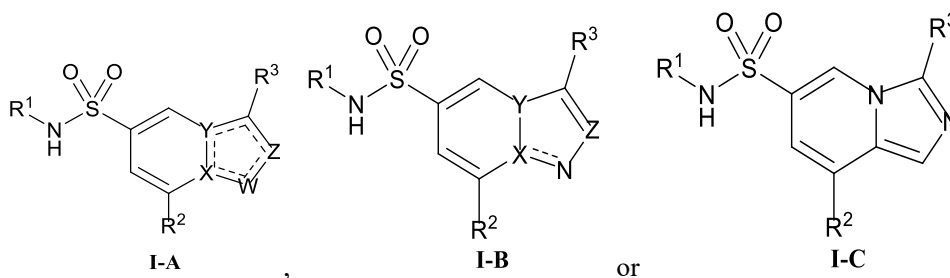
T₁ is C or N; and

T₂ is C or N; and

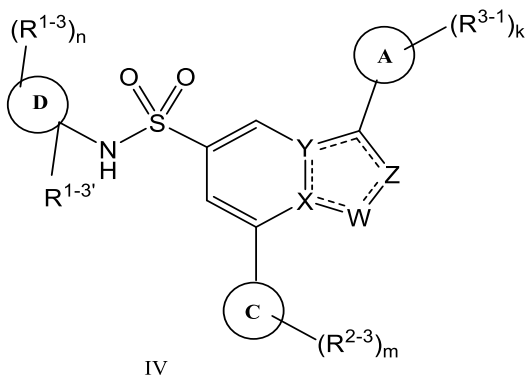
A, R¹, R², R³ and R⁴ are as previously defined.

In a preferred embodiment, at least one of T₁, T₂, X and Y is N, or Y, or Y, W and Z comprise only one heteroatom.

In a preferred embodiment, the compound of formula I-a can be a compound of formula I-A, formula I-B or



In a preferred embodiment, the compound of formula I-a can be a compound of formula IV,



ring D is 3-6 membered heterocycloalkyl; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3 (the 3-6 membered heterocycloalkyl in ring D is defined as in R¹);

ring C is 4-12 membered heterocycloalkyl; the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3 (the 4-12 membered heterocycloalkyl in ring C is defined as in R²);

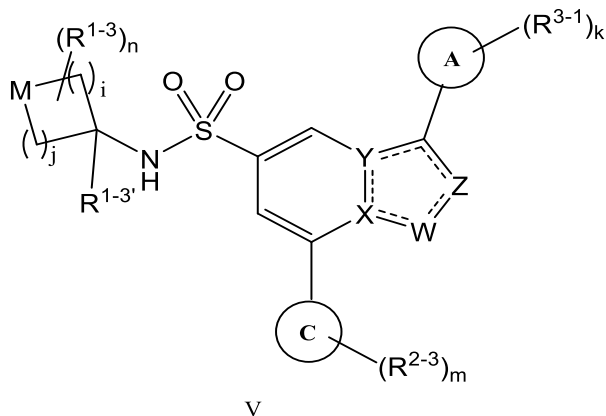
ring A is 5-10 membered heteroaryl; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3 (the 5-10 membered heteroaryl in ring A is defined as in R³);

n is 0, 1 or 2; m is 0, 1 or 2; k is 0, 1 or 2;

R^{1-3'} is hydrogen or R¹⁻³; and

R¹⁻³, R²⁻³ and R³⁻¹ are as previously defined.

In a preferred embodiment, the compound of formula I-a can be a compound of formula V,

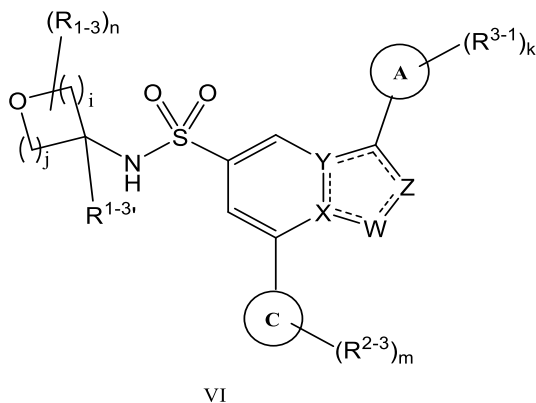


M is N, O or S;

i is 0, 1 or 2; j is 0, 1 or 2; i and j are not 0 at the same time; and

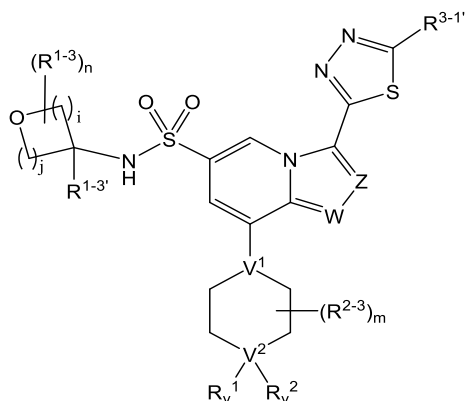
ring C, ring A, R^{1-3'}, R¹⁻³, R²⁻³, R³⁻¹, n, m and k are as previously defined.

In a preferred embodiment, the compound of formula I-a can be a compound of formula VI,



ring C, ring A, R^{1-3'}, R¹⁻³, R²⁻³, R³⁻¹, n, m, k, i and j are as previously defined.

In a preferred embodiment, the compound of formula I-a can be a compound of formula VII,



VII

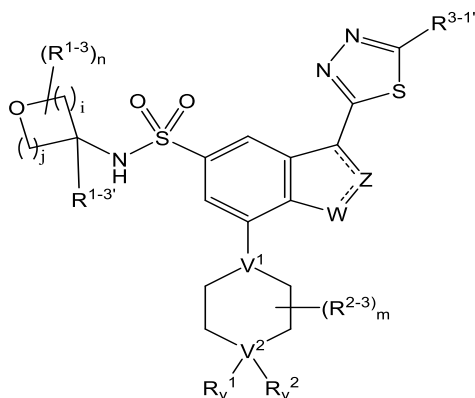
V^1 is CH, N or O; V^2 is CH, N or O; V^1 and V^2 are not CH at the same time;

$R^{3-1'}$ is hydrogen or R^{3-1} ; and

R_{V^1} is hydrogen or R^{2-3} ; R_{V^2} is hydrogen or R^{2-3} ; and

$R^{1-3'}$, R^{1-3} , R^{2-3} , R^{3-1} , n, m, i and j are as previously defined.

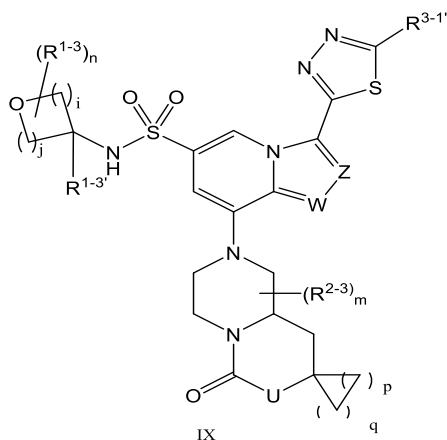
In a preferred embodiment, the compound of formula I-a can be a compound of formula VIII,



VIII

R_{V^1} , R_{V^2} , $R^{1-3'}$, R^{1-3} , R^{2-3} , $R^{3-1'}$, n, m, i and j are as previously defined.

In a preferred embodiment, the compound of formula I-a can be a compound of formula IX,



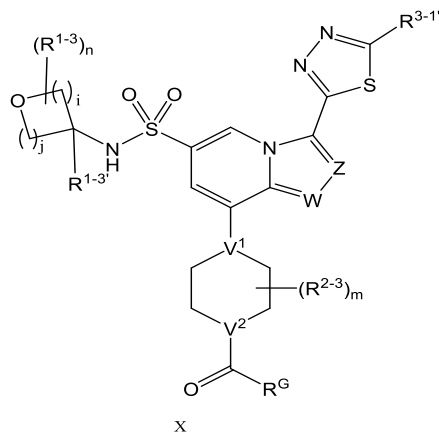
IX

U is CH, N or O;

p is 0, 1 or 2; q is 0, 1 or 2; and

$R^{1-3'}$, R^{1-3} , R^{2-3} , R^{3-1} , n , m , i and j are as previously defined.

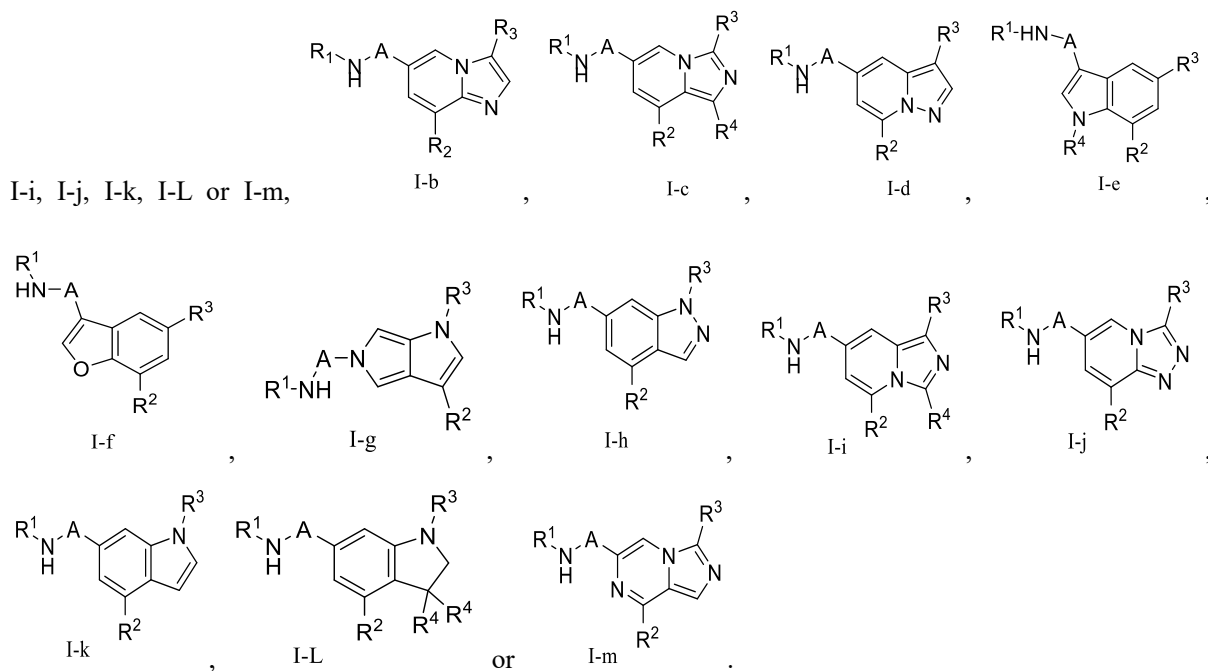
In a preferred embodiment, the compound of formula I-a can be a compound of formula X,



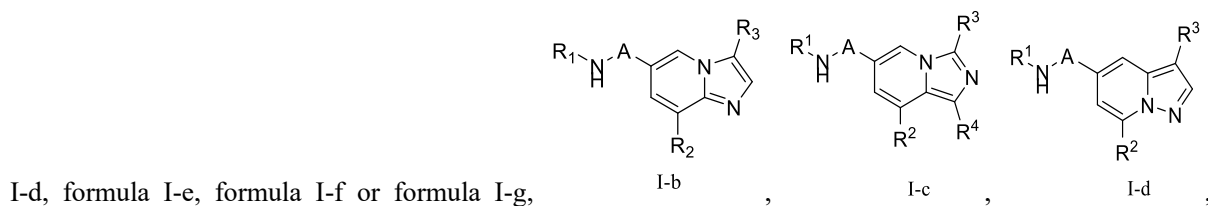
R^G is R^{2-3-2} or $\text{---}N(R^{2-3-3})_2$; and

$R^{1-3'}$, R^{1-3} , R^{2-3} , $R^{3-1'}$, R^{2-3-2} , R^{2-3-3} , V^1 , V^2 , n , m , i and j are as previously defined.

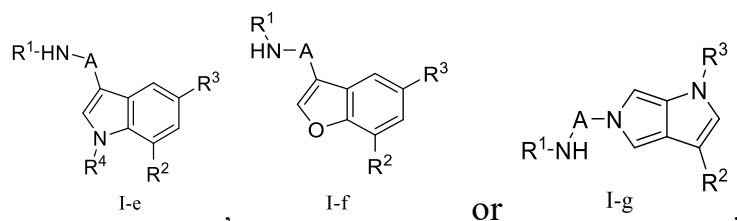
In a preferred embodiment, the compound of formula I is a compound of formula I-b, I-c, I-d, I-e, I-f, I-g, I-h,



In a preferred embodiment, the compound of formula I is a compound of formula I-b, formula I-c, formula

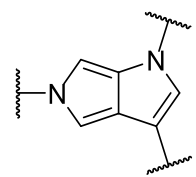


formula I-d, formula I-e, formula I-f or formula I-g,



In a preferred embodiment, in R^A , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

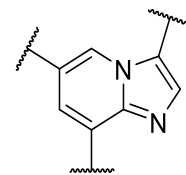
In a preferred embodiment, in ring B, the heteroatom in the 5-membered-fused 5-membered heteroaromatic



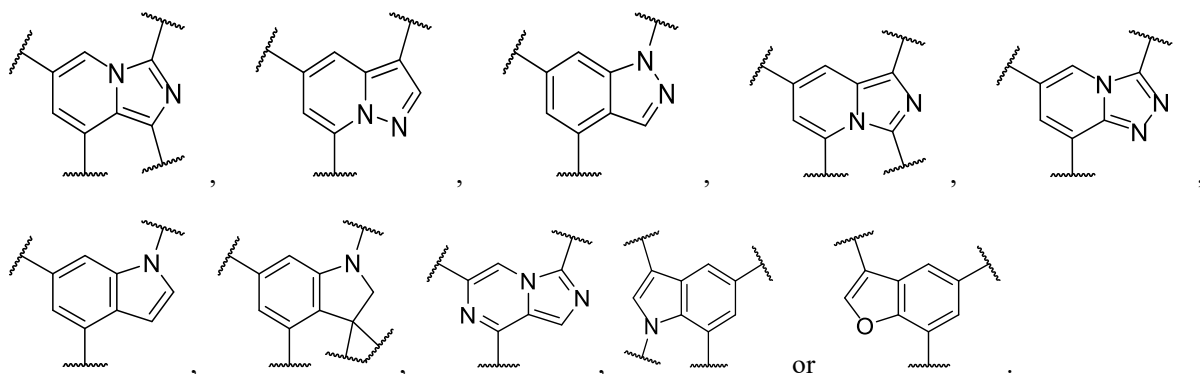
ring can be N, and the number of heteroatom(s) can be 1, 2 or 3, for example,

In a preferred embodiment, in ring B, the 3-6 membered cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl.

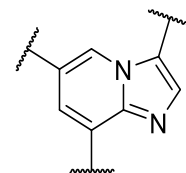
In a preferred embodiment, in ring B, the heteroatom in the 5-membered-fused 6-membered heteroaromatic



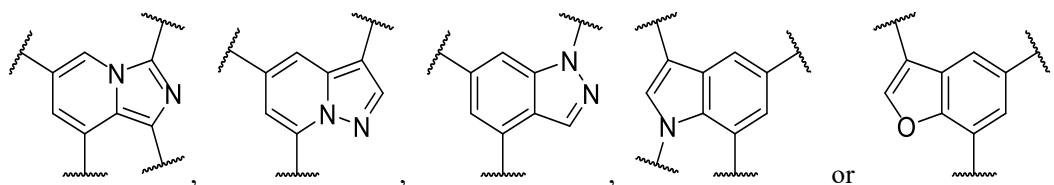
ring is N and/or O, and the number of heteroatom(s) can be 1, 2 or 3, for example,



In a preferred embodiment, in ring B, the heteroatom in the 5-membered-fused 6-membered heteroaromatic



ring can be N and/or O, and the number of heteroatom(s) can be 1, 2 or 3, for example,



In a preferred embodiment, in R^1 , the C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl, isopropyl or tert-butyl.

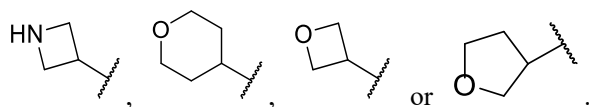
In a preferred embodiment, in R^1 , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl.

In a preferred embodiment, in R^1 , the C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

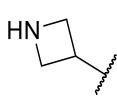
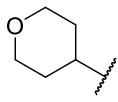


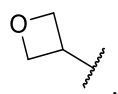
In a preferred embodiment, in R^1 , the C_3 - C_6 cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclopentane, for example, cyclopropyl, cyclobutane or bicyclopentane.

In a preferred embodiment, in R^1 , the heteroatom in the 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2; the heteroatom in the 3-6 membered heterocycloalkyl can be O or N, and the number of heteroatom can also be 1; azacyclobutane group, oxacyclobutane group, oxacyclo-azacyclobutanyl, oxacyclobutanyl, oxacyclopentanyl or oxacyclohexanyl is preferred, for example,

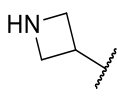
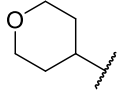


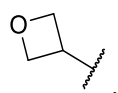
In a preferred embodiment, in R^1 , the heteroatom in the 3-6 membered heterocycloalkyl can be N, O or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in the 3-6 membered heterocycloalkyl can

also be O or N, and the number of heteroatom can also be 1, for example, ,  or



In a preferred embodiment, in R^{1-1} , the heteroatom in the 3-6 membered heterocycloalkyl can be N, O or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in the 3-6 membered heterocycloalkyl can

also be O or N, and the number of heteroatom can also be 1, for example, ,  or



In a preferred embodiment, in each R^{1-1} , the halogen can be fluorine, chlorine, bromine or iodine, for

example, fluorine.

In a preferred embodiment, in each R^{1-1} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl.

In a preferred embodiment, in each R^{1-1} , the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy.

In a preferred embodiment, in each R^{1-1} , the C_3 - C_6 cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

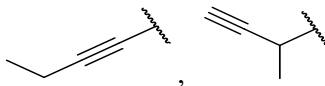
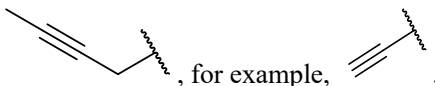
In a preferred embodiment, in each R^{1-1-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

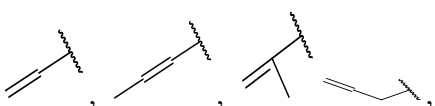
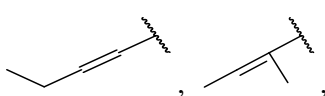
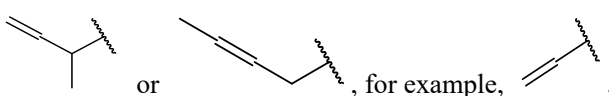
In a preferred embodiment, in each R^{1-1-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-1-3} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl.

In a preferred embodiment, in each R^{1-2} , the C_2 - C_6 alkynyl can be , , or , for example, .

In a preferred embodiment, in each R^{1-2} , the C_2 - C_6 alkenyl can be , , or , for example, .

In a preferred embodiment, in R^{1-2} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy.

In a preferred embodiment, in each R^{1-2-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2-1} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy or ethoxy.

In a preferred embodiment, in each $R^{1-2-1-1}$, the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2-2} , the halogen can be fluorine, chlorine, bromine or iodine, for

example, fluorine.

In a preferred embodiment, in each R^{1-2-2} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy or ethoxy.

In a preferred embodiment, in each $R^{1-2-2-1}$, the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2-3} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2-3} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy.

In a preferred embodiment, in each $R^{1-2-3-1}$, the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2-4} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2-4} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy or ethoxy.

In a preferred embodiment, in each $R^{1-2-4-1}$, the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-2-5} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl.

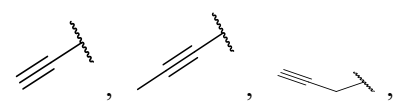
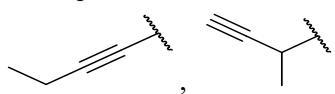
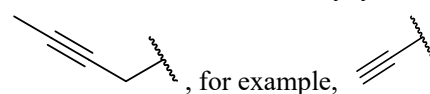
In a preferred embodiment, in each R^{1-2-5} , the C_3 - C_6 cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclopentane, for example, cyclopropyl, cyclobutane or bicyclopentane.

In a preferred embodiment, in $R^{1-2-5-1}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl.

In a preferred embodiment, in each R^{1-3} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-3} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{1-3} , the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy.

In a preferred embodiment, in each R^{1-3} , the C_2 - C_6 alkynyl is , , or , for example, .

In a preferred embodiment, in each R^{1-3-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{1-3-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

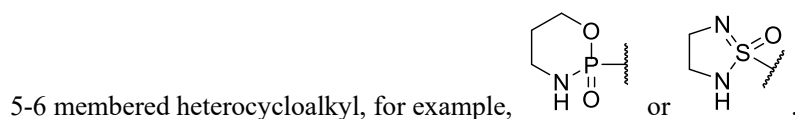
In a preferred embodiment, in R^{1-4} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{1-5} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{1-5} , the C_3-C_6 cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclopentane, for example, cyclopropyl, cyclobutane or bicyclopentane.

In a preferred embodiment, in R^{1-5-1} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, the atom in R^1 , when attached to the atom in A, forms 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 ; the 5-10 membered heterocycloalkyl can be



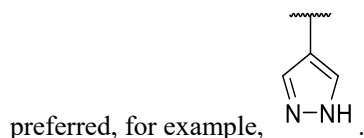
In a preferred embodiment, in each R^0 , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in R^2 , the 6-10 membered aryl can be phenyl or naphthyl, for example, phenyl.

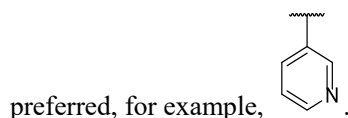
In a preferred embodiment, in R^2 , the 5-10 membered heteroaryl is 5 or 6 membered heteroaryl, or 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3.

In a preferred embodiment, in R^2 , the 5-10 membered heteroaryl can be 5 or 6 membered heteroaryl, 5-membered-fused 5-membered heteroaryl, or 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3.

The heteroatom in the 5 membered heteroaryl can be N, the number of heteroatoms is 2, pyrazolyl is



The heteroatom in the 6 membered heteroaryl can be N, the number of heteroatom(s) is 1, and pyridyl is

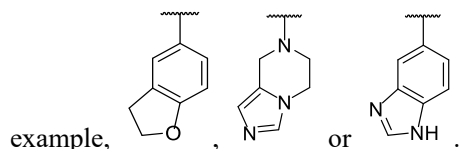


The heteroatom in the 5-membered-fused 5-membered heteroaryl can be N, the number of heteroatoms is 3,



and dihydropyrrolopyrazolyl is preferred, for example,

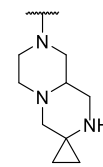
The heteroatom in the 5-membered-fused 6-membered heteroaryl can be N and/or O, the number of heteroatom(s) is 1, 2 or 3, and benzofuryl, dihydroimidazopyrazinyl or benzoimidazolyl is preferred, for



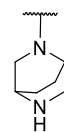
In a preferred embodiment, in R^2 , the 5-10 membered heteroaryl can be 5 or 6 membered heteroaryl, or 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is one or more selected from N and/or S, and the number of heteroatom(s) is 1 or 2. The heteroatom in the 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms is 2. The heteroatom in the 6 membered heteroaryl can be N, and the number of heteroatom(s) is 1 or 2. The heteroatom in the 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3.

In a preferred embodiment, in R^2 , the 4-12 membered heterocycloalkyl is one or more selected from a monocyclic ring, a bridged ring, a fused ring and a spiro ring. The monocyclic ring can be 4-6 membered heterocycloalkyl. The fused ring can be 5-membered-fused 6-membered heterocycloalkyl, 4-membered-fused 6-membered heterocycloalkyl or 5-membered-fused 5-membered heterocycloalkyl. The spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring, 4 membered-spiro 4-membered ring, 5 membered-spiro 6-membered ring or 3 membered-spiro 6-membered ring. The bridged ring can be bicycloheterooctane or bicycloheteroheptane. The heteroatom in the 4-12 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1, 2 or 3.

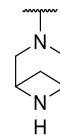
The 4-12 membered heterocycloalkyl can be 3-membered -spiro 6-membered-fused 6-membered



heterocycloalkyl, preferably, hexahydro-spiro-cyclopropan-pyrazinopyrazinyl, for example,

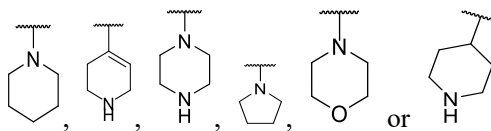


The bicycloheterooctane can be bicyclo[2.2.2]heterooctane, for example,



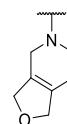
The bicycloheteroheptane can be bicyclo[3.1.1]heteroheptane, for example,

The 4-6 membered heterocycloalkyl can be azacyclohexanyl, tetrahydropyridyl, piperazinyl,

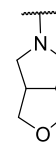
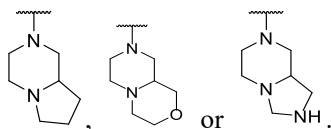


azacyclopentanyl or morpholinyl, for example,

The 5-membered-fused 6-membered heterocycloalkyl can be tetrahydrofuranopyridyl,

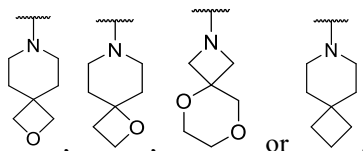


hexahydropyrrolopyrazinyl, hexahydropyrazinooxazinyl or hexahydroimidazopyrazinyl, for example,

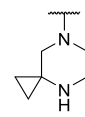


The 5-membered-fused 5-membered heterocycloalkyl can be tetrahydrofuranopyrrolyl, for example,

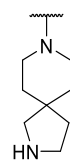
The 4 membered-spiro 6-membered ring can be oxaaza-spiro-nonanyl, dioxaza-spiro-nonanyl or



aza-spiro-nonanyl, for example,



The 3 membered-spiro 6-membered ring can be diaza-spiro-octanyl, for example,



The 5 membered-spiro 6-membered ring can be diaza-spiro-decanyl, for example,

In a preferred embodiment, in R^2 , the 4-12 membered heterocycloalkyl is saturated heterocycloalkyl, or heterocycloalkyl containing 1-2 double bond(s).

In a preferred embodiment, in R^2 , the 4-10 membered heterocycloalkyl can be a monocyclic ring, a bridged ring, a fused ring or a spiro ring. The monocyclic ring can be 4-6 membered heterocycloalkyl. The fused ring can be 5-membered-fused 6-membered heterocycloalkyl or 4-membered-fused 6-membered heterocycloalkyl. The spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring or 4 membered-spiro 4-membered ring. The heteroatom in the 4-10 membered heterocycloalkyl is selected from

N and/or O, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in R^2 , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in R^2 , the C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopentyl.

In a preferred embodiment, in R^2 , the C_3 - C_6 cycloalkenyl can be cycloalkenyl containing 1 double bond, or



can be 5 membered cycloalkenyl, for example, .

In a preferred embodiment, in each R^{2-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-1} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-1} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy.

In a preferred embodiment, in each R^{2-1-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-1-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-1-3} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-1-4} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in each R^{2-2} , the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy.

In a preferred embodiment, in each R^{2-2-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-2-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-2-3} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-2-4} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

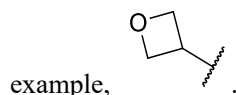
In a preferred embodiment, in each R^{2-2-4} , the C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl.

In a preferred embodiment, in each R^{2-3} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-3} , the C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl, isopropyl or tert-butyl.

In a preferred embodiment, in each R^{2-3} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-3} , the heteroatom in the 3-6 membered heterocycloalkyl can be N, O or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in the 3-6 membered heterocycloalkyl can also be O or N, and the number of heteroatom(s) can also be 1; and oxacyclobutanyl s preferred, for



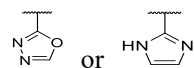
In a preferred embodiment, in each R^{2-3} , the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy, ethoxy or isopropoxy.

In a preferred embodiment, in each R^{2-3} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy or ethoxy.

In a preferred embodiment, in each R^{2-3} , the C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl.

In a preferred embodiment, in each R^{2-3} , the 5-10 membered heteroaryl is 5 membered heteroaryl or 6 membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1, 2, or 3. The heteroatom in the 5 membered heteroaryl can be N and/or O, the number of

heteroatom(s) is 2 or 3, and triazolyl, oxadiazolyl, or imidazolyl is preferred, for example, , ,



The heteroatom in the 6 membered heteroaryl can be N, the number of heteroatom(s) is 1

or 2, and pyridyl is preferred, for example, .

In a preferred embodiment, in each R^{2-3-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-3-1} , the C_1 - C_6 alkoxy can be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy or ethoxy.

In a preferred embodiment, in each R^{2-3-1} , the C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or

cyclohexyl, for example, cyclopropyl.

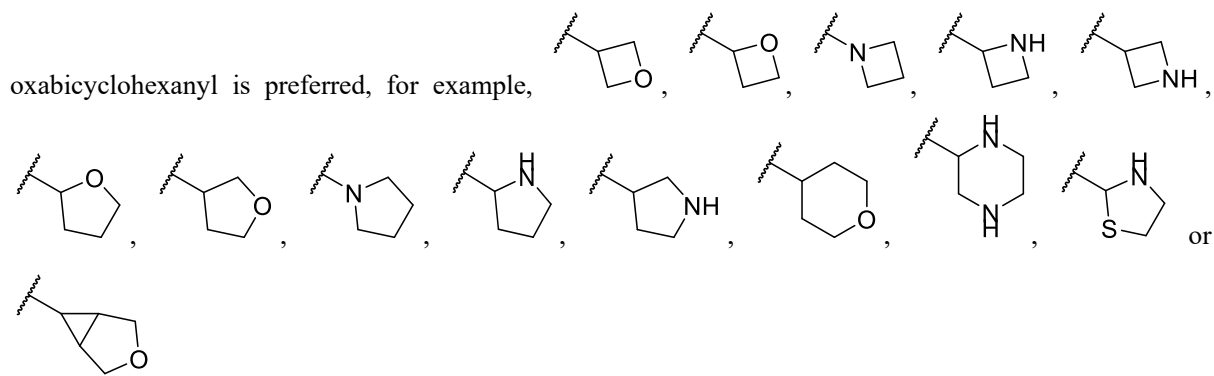
In a preferred embodiment, in each R^{2-3-2} , the C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl, isopropyl or tert-butyl.

In a preferred embodiment, in R^{2-3-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in R^{2-3-2} , the C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl or cyclobutyl.

In a preferred embodiment, in R^{2-3-2} , the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, isopropoxy.

In a preferred embodiment, in R^{2-3-2} , the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) can be 1 or 2; oxacyclobutanyl, azacyclobutanyl, oxacyclopentanyl, azacyclopentanyl, oxacyclohexanyl, azacyclohexanyl, pyrazinyl, thiazolidinyl or



In a preferred embodiment, in R^{2-3-2} , the 5-10 membered heteroaryl is 5 or 6 membered heteroaryl, or 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2. The heteroatom in the 5 membered heteroaryl can be N and/or O, and the number of heteroatoms is 2. The heteroatom in the 6 membered heteroaryl can be N, and the number of heteroatom(s) is 1. The heteroatom in the 5-membered-fused 6-membered heteroaryl can be O, and the number of heteroatoms is 2.

In a preferred embodiment, in each R^{2-3-3} , the C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl or ethyl.

In a preferred embodiment, in each R^{2-3-3} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-3-4} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be isopropyl.

In a preferred embodiment, in each R^{2-3-5} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-3-6} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can be methyl, ethyl,

n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each R^{2-3-7} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each R^{2-3-8} , the C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl or isopropyl.

In a preferred embodiment, in each R^{2-3-8} , the C_3-C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl.

In a preferred embodiment, in each R^{2-3-9} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each $R^{2-3-1-1}$, the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-1-2}$, the C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy.

In a preferred embodiment, in each $R^{2-3-1-3}$, the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each $R^{2-3-2-1}$, the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-2-1}$, the C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy.

In a preferred embodiment, in each $R^{2-3-2-1}$, the 5-10 membered heteroaryl is 5 membered heteroaryl. The heteroatom in the 5 membered heteroaryl can be N, and the number of heteroatoms is 3.

In a preferred embodiment, in each $R^{2-3-2-1-1}$, the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each $R^{2-3-2-1-1}$, the 6-10 membered aryl can be phenyl or naphthyl, for example, phenyl.

In a preferred embodiment, in each $R^{2-3-2-1-2}$, the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each $R^{2-3-2-1-3}$, the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each $R^{2-3-2-2}$, the halogen is fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-2-2}$, the C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each $R^{2-3-2-2}$, the C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy, ethoxy or n-propoxy. In a

preferred embodiment, in each $R^{2-3-2-2-1}$, the halogen is fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-2-2-2}$, the halogen is fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-2-2-3}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each $R^{2-3-2-3-1}$, the 6-10 membered aryl is phenyl or naphthyl, for example, phenyl.

In a preferred embodiment, in each $R^{2-3-2-3-1-1}$, the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy.

In a preferred embodiment, in each $R^{2-3-2-4}$, the halogen is fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-2-5}$, the halogen is fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-2-5}$, the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy.

In a preferred embodiment, in each $R^{2-3-2-5}$, the C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl, ethyl, n-propyl or isopropyl.

In a preferred embodiment, in each $R^{2-3-2-5-1}$, the halogen is fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each $R^{2-3-2-6}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each $R^{2-3-3-1-1}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each R^{2-4} , the 4-10 membered heterocycloalkyl can be a monocyclic ring. The 4-10 membered heterocycloalkyl can be 4-6 membered heterocycloalkyl. The heteroatom in the 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in each R^{2-4} , the 5-10 membered heteroaryl can be 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3.

In a preferred embodiment, in each R^{2-4} , the 6-10 membered aryl can be phenyl or naphthyl, for example, phenyl.

In a preferred embodiment, in each R^{2-4} , the C_3 - C_6 cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopentyl.

In a preferred embodiment, in each R^{2-4-1} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-4-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-4-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-4-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-4-3} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-4-3} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-4-4} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-4-4} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in $R^{2-4-1-1}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in each $R^{2-4-1-2}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in each R^{2-5} , the 4-10 membered heterocycloalkyl can be a monocyclic ring. The 4-10 membered heterocycloalkyl can be 4-6 membered heterocycloalkyl. The heteroatom in the 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in each R^{2-5} , the 6-10 membered aryl is phenyl or naphthyl, for example, phenyl.

In a preferred embodiment, in each R^{2-5} , the C_1 - C_6 alkyl is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in $R^{2-5-1-1}$, the C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in $R^{2-5-1-1}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each $R^{2-5-1-2}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in R^{2-5-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in each R^{2-5-3} , the C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy,

n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy.

In a preferred embodiment, in each R^{2-6} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-6} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-6} , the 4-10 membered heterocycloalkyl can be a monocyclic ring. The 4-10 membered heterocycloalkyl can be 4-6 membered heterocycloalkyl. The heteroatom in the 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in each R^{2-6} , the 5-10 membered heteroaryl can be 5-6 membered heteroaryl. The heteroatom in the 5-6 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in each R^{2-6-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-6-1} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in $R^{2-6-1-1}$, the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-6-2} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in each R^{2-6-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-7} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-7} , the 4-10 membered heterocycloalkyl can be a monocyclic or spiro ring. The monocyclic ring can be 4-6 membered heterocycloalkyl. The spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring or 4 membered-spiro 4-membered ring. The heteroatom in the 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in each R^{2-7} , the 5-10 membered heteroaryl can be 5 or 6 membered heteroaryl, or 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is one or more selected from N and/or S, and the number of heteroatom(s) is 1 or 2. The heteroatom in the 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms is 2. The heteroatom in the 6 membered heteroaryl can be N, and the number of heteroatom(s) is 1 or 2. The heteroatom in the 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3.

In a preferred embodiment, in each R^{2-7-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{2-7-1} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in $R^{2-7-1-1}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in $R^{2-7-1-2}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-7-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

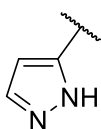
In a preferred embodiment, in each R^{2-7-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-8} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-8} , the 4-10 membered heterocycloalkyl can be a monocyclic ring. The monocyclic ring can be 4-6 membered heterocycloalkyl. The heteroatom in the 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1 or 2.

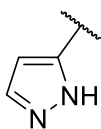
In a preferred embodiment, in each $R^{2-8-1-1}$, the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{2-9} , the 5-10 membered heteroaryl is 5 membered heteroaryl; the heteroatom in the 5-10 membered heteroaryl is N and/or S, and the number of heteroatom(s) is 1 or 2; the heteroatom in the 5 membered heteroaryl can be N, and the number of heteroatoms is 2; pyrazolyl is



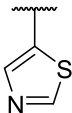
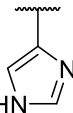
preferred, for example,

In a preferred embodiment, in each R^{2-10} , the 5-10 membered heteroaryl is 5 membered heteroaryl; the heteroatom in the 5-10 membered heteroaryl is N and/or S, and the number of heteroatom(s) is 1 or 2; the heteroatom in the 5 membered heteroaryl can be N, and the number of heteroatoms is 2; pyrazolyl is

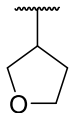


preferred, for example,

In a preferred embodiment, in each R^{2-11} , the 5-10 membered heteroaryl is 5 membered heteroaryl. The heteroatom in the 5 membered heteroaryl can be N and/or S, and the number of heteroatoms is 2; and

thiazolyl or imidazolyl is preferred, for example,  or .

In a preferred embodiment, in each R^{2-11} , the heteroatom in the 3-6 membered heterocycloalkyl is O, and the

number of heteroatom(s) can be 1; and oxacyclopentanyl is preferred, for example, .

In a preferred embodiment, in each R^{2-11-1} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in each R^{2-11-2} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl.

In a preferred embodiment, in R^3 , the 5-10 membered heteroaryl is 5 membered heteroaryl, 5-membered-fused 5-membered heteroaryl, or 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is N and/or S, and the number of heteroatom(s) is 1, 2, or 3. The heteroatom in the 5 membered heteroaryl can be N and/or S, and the number of heteroatom(s) is 2 or 3. The heteroatom in the 5-membered-fused 6-membered heteroaryl can be N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3. The heteroatom in the 5-membered-fused 5-membered heteroaryl can be N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3.

In a preferred embodiment, in R^3 , the 5-10 membered heteroaryl can be 5 membered heteroaryl, 5-membered-fused 5-membered heteroaryl, or 5-membered-fused 6-membered heteroaryl. The heteroatom in the 5-10 membered heteroaryl is one or more selected from N and/or S, and the number of heteroatom(s) is 1 or 2. The heteroatom in the 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms is 2. The heteroatom in the 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3. The heteroatom in the 5-membered-fused 5-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3.

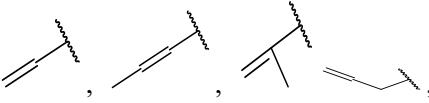
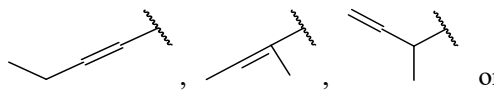
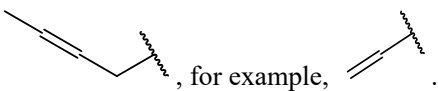
In a preferred embodiment, in R^3 , the 3-10 membered heterocycloalkyl can be a monocyclic ring. The monocyclic ring can be 4-6 membered heterocycloalkyl. The heteroatom in the 3-10 membered heterocycloalkyl is selected from N, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in each R^{3-1} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{3-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in each R^{3-1-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in R^{3-1-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or ethyl.

In a preferred embodiment, in R^{3-1-2} , the C_2 - C_6 alkenyl can be , , or , for example, .

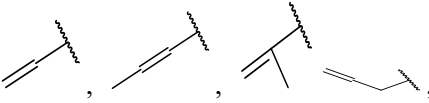
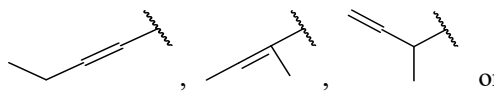
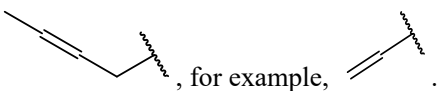
In a preferred embodiment, in R^{3-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in R^{3-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in R^{3-2-1} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in R^{3-2-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or ethyl.

In a preferred embodiment, in R^{3-2-2} , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in R^{3-2-2} , the C_2 - C_6 alkenyl can be , , or , for example, .

In a preferred embodiment, in R^{4-2} , the halogen is fluorine, chlorine, bromine or iodine, for example, fluorine or chlorine.

In a preferred embodiment, in R^{4-2} , the halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine.

In a preferred embodiment, in R^{4-7} , the 4-10 membered heterocycloalkyl is a monocyclic or spiro ring. The monocyclic ring can be 6 membered heterocycloalkyl. The spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring or 4 membered-spiro 4-membered ring. The heteroatom in the 4-10 membered heterocycloalkyl can be N, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in R^4 , the 5-10 membered heterocycloalkyl can be a spiro ring. The spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring or 4 membered-spiro 4-membered ring. The heteroatom in the 4-10 membered heterocycloalkyl can be N, and the number of heteroatom(s) is 1 or 2.

In a preferred embodiment, in R^4 , the C_1 - C_6 alkyl can be C_1 - C_4 alkyl, and can also be methyl, ethyl, n-propyl,

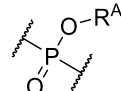
isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{4-2} , the 5-10 membered heteroaryl is 5 membered heteroaryl. The heteroatom in the 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms is 2.

In a preferred embodiment, in R^{4-1-1} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl.

In a preferred embodiment, in each R^{4-1-2} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

In a preferred embodiment, in each R^{4-2-1} , the C_1-C_6 alkyl can be C_1-C_4 alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

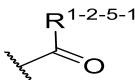
In a preferred embodiment, A is ,  or ; R^A is hydrogen or C_1-C_6 alkyl;

ring B is a 5-membered-fused 6-membered heteroaromatic ring unsubstituted or substituted by R^B ; the heteroatom in the 5-membered-fused 6-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; when the heteroatom in the 5-membered-fused 6-membered heteroaromatic ring is only nitrogen, in the 5-membered-fused 6-membered heteroaromatic ring, at least one of 6 members is N or 5 members comprise only one N; R^B is each independently selected from oxo, hydroxyl, halogen or C_1-C_6 alkyl;

R^1 is hydroxyl, C_1-C_6 alkyl unsubstituted or substituted by one or more R^{1-1} , C_3-C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} , or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{1-1} is each independently selected from deuterium, hydroxyl, cyano, halogen or C_3-C_6 cycloalkyl;

R^{1-2} is each independently selected from deuterium, hydroxyl, cyano, halogen, C_1-C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} , C_2-C_6 alkynyl, C_1-C_6 alkoxy unsubstituted or substituted by one or more R^{1-2-3} or amino unsubstituted or substituted by one or two R^{1-2-5} ; R^{1-2-1} is each independently selected from halogen, hydroxyl or C_1-C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-1-1}$; $R^{1-2-1-1}$ is each independently halogen; R^{1-2-3} is each independently halogen; R^{1-2-5} is each independently selected from

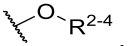
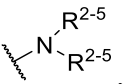
C_1-C_6 alkyl,  or C_3-C_6 cycloalkyl; $R^{1-2-5-1}$ is C_1-C_6 alkyl or amino;

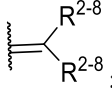
R^{1-3} is each independently C_1-C_6 alkyl;

or, the atom in R^1 is attached to the atom in A to form 5-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 ; the heteroatom in the 5-6 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from

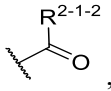
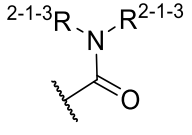
C₁-C₆ alkyl or oxo;

R² is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R²⁻¹, 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻², 4-10 membered heterocycloalkyl unsubstituted

or substituted by one or more R²⁻³, , , C₁-C₆ alkyl unsubstituted or substituted by one

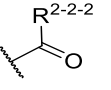
or more R²⁻⁶,  or ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻¹ is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or

more R²⁻¹⁻¹, ,  or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻¹⁻⁴;

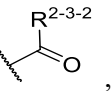
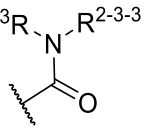
R²⁻¹⁻¹ is each independently selected from cyano or halogen; R²⁻¹⁻² is hydrogen or C₁-C₆ alkyl; R²⁻¹⁻³ is each independently selected from hydrogen or C₁-C₆ alkyl; R²⁻¹⁻⁴ is each independently halogen;

R²⁻² is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or

more R²⁻²⁻¹, , ;

R²⁻²⁻¹ is each independently selected from cyano or halogen; R²⁻²⁻² is hydrogen or C₁-C₆ alkyl; R²⁻²⁻³ is each independently selected from hydrogen or C₁-C₆ alkyl;

R²⁻³ is each independently selected from cyano, oxo, hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or

substituted by one or more R²⁻³⁻¹, , , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³⁻⁴, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻⁵; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³⁻¹ is each independently selected from cyano, halogen, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹;

R²⁻³⁻² is hydrogen or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻¹;

R²⁻³⁻³ is each independently hydrogen or C₁-C₆ alkyl;

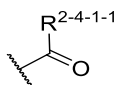
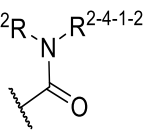
R^{2-3-4} is each independently C_1 - C_6 alkyl;

R^{2-3-5} is each independently halogen;

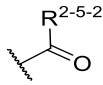
$R^{2-3-1-1}$ is each independently halogen;

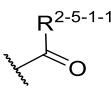
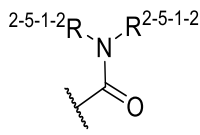
$R^{2-3-2-1}$ is each independently halogen;

各 R^{2-4} is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} or C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{2-4-4} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^{2-4-1} is each independently selected from hydroxyl, halogen, C_1 - C_6

alkyl,  or ; R^{2-4-2} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-4} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; $R^{2-4-1-1}$ is C_1 - C_6 alkyl; each $R^{2-4-1-2}$ is C_1 - C_6 alkyl;

R^{2-5} is each independently hydrogen, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or

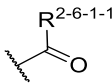
more R^{2-5-1} , or ; the heteroatom in the 4-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-5-1} is each independently selected from  or ; $R^{2-5-1-1}$ is hydrogen or C_1 - C_6 alkyl;

$R^{2-5-1-2}$ is each independently selected from hydrogen or C_1 - C_6 alkyl;

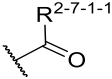
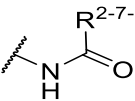
R^{2-5-2} is C_1 - C_6 alkyl;

R^{2-6} is each independently selected from halogen, C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1 - C_6 alkyl or ; $R^{2-6-1-1}$ is C_1 - C_6 alkyl; R^{2-6-2} is each independently selected from halogen or C_1 - C_6 alkyl;

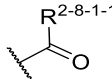
R^{2-7} is C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in the 4-10

membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-7-1} is each independently selected from halogen, C_1-C_6 alkyl,  or ; $R^{2-7-1-1}$ is C_1-C_6 alkyl; $R^{2-7-1-2}$ is C_1-C_6 alkyl;

R^{2-7-2} is each independently selected from halogen or C_1-C_6 alkyl;

R^{2-8} is each independently C_1-C_6 alkyl, or two R^{2-8} , together with the atom to which they are attached, form 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

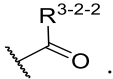
R^{2-8-1} is each independently ; and $R^{2-8-1-1}$ is hydrogen or C_1-C_6 alkyl.

R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{3-1} is each independently selected from hydroxyl, halogen, C_1-C_6 alkyl unsubstituted or substituted by one or more R^{3-1-1} ;

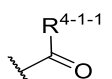
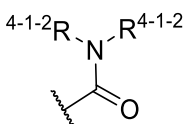
R^{3-1-1} is each independently halogen;

R^{3-2} is each independently selected from hydroxyl, halogen, C_1-C_6 alkyl unsubstituted or substituted by one

or more R^{3-2-1} or ;

R^{3-2-1} is each independently halogen; R^{3-2-2} is C_1-C_6 alkyl or C_2-C_4 alkenyl;

R^4 is hydrogen, halogen, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} or C_1-C_6 alkyl unsubstituted or substituted by one or more R^{4-2} ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{4-1} is each independently  or ;

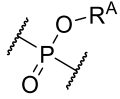
R^{4-2} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{4-2-1} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R^{4-1-1} is C_1 - C_6 alkyl; R^{4-1-2} is each independently C_1 - C_6 alkyl; R^{4-2-1} is each independently C_1 - C_6 alkyl.

In a preferred embodiment, Y is C or N, X is C or N, and at least one of X and Y is N;

W is N, CH or CR^4 ;

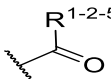
Z is CH or N;

A is ,  or ; R^A is hydrogen or C_1 - C_6 alkyl;

R^1 is hydroxyl, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1} , C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} , or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{1-1} is each independently selected from deuterium, hydroxyl, cyano, halogen or C_3 - C_6 cycloalkyl;

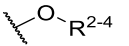
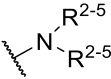
R^{1-2} is each independently selected from deuterium, hydroxyl, cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} , C_2 - C_6 alkynyl, C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-2-3} or amino unsubstituted or substituted by one or two R^{1-2-5} ; R^{1-2-1} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-1-1}$; $R^{1-2-1-1}$ is each independently halogen; R^{1-2-3} is each independently halogen; R^{1-2-5} is each independently selected from

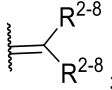
C_1 - C_6 alkyl,  or C_3 - C_6 cycloalkyl; $R^{1-2-5-1}$ is C_1 - C_6 alkyl or amino;

R^{1-3} is each independently C_1 - C_6 alkyl;

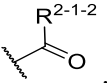
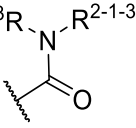
or, the atom in R^1 is attached to the atom in A to form 5-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 ; the heteroatom in the 5-6 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from C_1 - C_6 alkyl or oxo;

R^2 is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-2} , 4-10 membered heterocycloalkyl unsubstituted

or substituted by one or more R^{2-3} , , , C_1 - C_6 alkyl unsubstituted or substituted by one

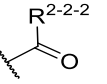
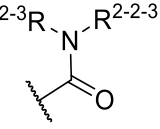
or more R^{2-6} ,  or ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-1} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

more R^{2-1-1} , ,  or C₁-C₆ alkoxy unsubstituted or substituted by one or more R^{2-1-4} ;

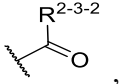
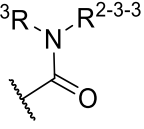
R^{2-1-1} is each independently selected from cyano or halogen; R^{2-1-2} is hydrogen or C₁-C₆ alkyl; R^{2-1-3} is each independently selected from hydrogen or C₁-C₆ alkyl; R^{2-1-4} is each independently halogen;

R^{2-2} is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or

more R^{2-2-1} ,  or  ;

R^{2-2-1} is each independently selected from cyano or halogen; R^{2-2-2} is hydrogen or C₁-C₆ alkyl; R^{2-2-3} is each independently selected from hydrogen or C₁-C₆ alkyl;

R^{2-3} is each independently selected from cyano, oxo, hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or

substituted by one or more R^{2-3-1} , , , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3-4} , C₁-C₆ alkoxy unsubstituted or substituted by one or more R^{2-3-5} ; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-1} is each independently selected from cyano, halogen, or C₁-C₆ alkoxy unsubstituted or substituted by one or more $R^{2-3-1-1}$;

R^{2-3-2} is hydrogen or C₁-C₆ alkyl unsubstituted or substituted by one or more $R^{2-3-2-1}$;

R^{2-3-3} is each independently hydrogen or C₁-C₆ alkyl;

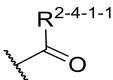
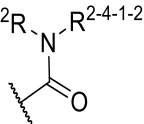
R^{2-3-4} is each independently C₁-C₆ alkyl;

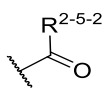
R^{2-3-5} is each independently halogen;

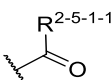
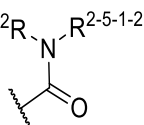
$R^{2-3-1-1}$ is each independently halogen;

$R^{2-3-2-1}$ is each independently halogen;

each R^{2-4} is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R^{2-4-4} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-4-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl,  or  ;
 R^{2-4-2} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-4} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; $R^{2-4-1-1}$ is C_1 - C_6 alkyl; $R^{2-4-1-2}$ is C_1 - C_6 alkyl;

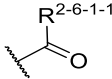
R^{2-5} is each independently hydrogen, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-5-1} , or  ; the heteroatom in the 4-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-5-1} is each independently selected from  or  ;
 $R^{2-5-1-1}$ is hydrogen or C_1 - C_6 alkyl;

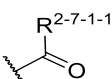
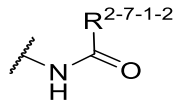
$R^{2-5-1-2}$ is each independently selected from hydrogen or C_1 - C_6 alkyl;

R^{2-5-2} is C_1 - C_6 alkyl;

R^{2-6} is each independently selected from halogen, C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1 - C_6 alkyl or  ; $R^{2-6-1-1}$ is C_1 - C_6 alkyl;
 R^{2-6-2} is each independently selected from halogen or C_1 - C_6 alkyl;

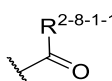
R^{2-7} is C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-7-1} is each independently selected from halogen, C_1 - C_6 alkyl,  or  ; $R^{2-7-1-1}$ is C_1 - C_6 alkyl; $R^{2-7-1-2}$ is C_1 - C_6 alkyl;

R^{2-7-2} is each independently selected from halogen or C_1 - C_6 alkyl;

R^{2-8} is each independently C_1 - C_6 alkyl, or two R^{2-8} , together with the atom to which they are attached, form

4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in the 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

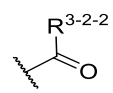
R^{2-8-1} is each independently ; and $R^{2-8-1-1}$ is hydrogen or C_1-C_6 alkyl.

R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{3-1} is each independently selected from hydroxyl, halogen, C_1-C_6 alkyl unsubstituted or substituted by one or more R^{3-1-1} ;

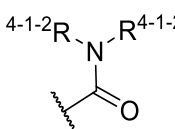
R^{3-1-1} is each independently halogen;

R^{3-2} is each independently selected from hydroxyl, halogen, C_1-C_6 alkyl unsubstituted or substituted by one

or more R^{3-2-1} or ;

R^{3-2-1} is each independently halogen; R^{3-2-2} is C_1-C_6 alkyl or C_2-C_4 alkenyl;

R^4 is hydrogen, halogen, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} or C_1-C_6 alkyl unsubstituted or substituted by one or more R^{4-2} ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{4-1} is each independently  or ;

R^{4-2} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{4-2-1} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R^{4-1-1} is C_1-C_6 alkyl; R^{4-1-2} is each independently C_1-C_6 alkyl; R^{4-2-1} is each independently C_1-C_6 alkyl.

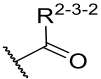
In an embodiment, R^1 is C_3-C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in the 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1;

R^{1-2} is each independently selected from cyano or C_1-C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} ; R^{1-2-1} is each independently halogen;

R^{1-3} is each independently C_1-C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} ; R^{1-3-1} is each independently halogen;

R^2 is hydrogen or 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the

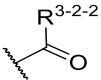
heteroatom in the 4-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2;

R^{2-3} is each independently  ;

R^{2-3-2} is C₁-C₆ alkyl;

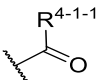
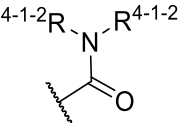
R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{5-2} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heterocycloalkyl is N, O and S, and the number of heteroatom(s) is 1 or 2; R^{3-1} is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R^{3-1-1} ;

R^{3-1-1} is each independently halogen;

R^{3-2} is each independently  ;

R^{3-2-2} is C₁-C₆ alkyl or C₂-C₄ alkenyl;

R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in the 5-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1, 2 or 3;

R^{4-1} is each independently  or  ;

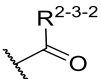
R^{4-1-1} is C₁-C₆ alkyl;

R^{4-1-2} is each independently C₁-C₆ alkyl.

In an embodiment, R^1 is C₃-C₆ cycloalkyl or 4 membered heterocycloalkyl, unsubstituted or substituted by one or more R^{1-2} ; the heteroatom in the 4 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1;

R^{1-2} is each independently selected from cyano or C₁-C₆ alkyl unsubstituted or substituted by one or more R^{1-2-1} ; R^{1-2-1} is each independently halogen;

R^2 is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in the 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

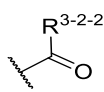
R^{2-3} is each independently  ;

R^{2-3-2} is C₁-C₆ alkyl;

R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 5-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1;

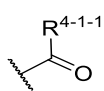
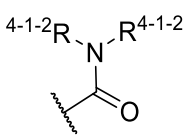
R³⁻¹ is each independently selected from halogen, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R³⁻² is each independently  ;

R³⁻²⁻² is C₂-C₄ alkenyl;

R⁴ is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁴⁻¹; the heteroatom in the 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

R⁴⁻¹ is each independently  or  ;

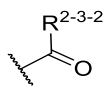
R⁴⁻¹⁻¹ is C₁-C₆ alkyl;

R⁴⁻¹⁻² is each independently C₁-C₆ alkyl.

In an embodiment, R¹ is C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻²;

R¹⁻² is each independently selected from cyano or C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻²⁻¹; R¹⁻²⁻¹ is each independently halogen;

R² is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in the 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

R²⁻³ is each independently  ;

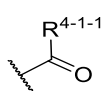
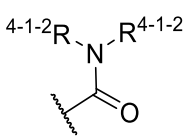
R²⁻³⁻² is C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently selected from halogen, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R⁴ is 7-9 membered heterocycloalkyl unsubstituted or substituted by one or more R⁴⁻¹; the heteroatom in the 7-9 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1;

R⁴⁻¹ is each independently  or  ;

R⁴⁻¹⁻¹ is C₁-C₆ alkyl;

R⁴⁻¹⁻² is each independently C₁-C₆ alkyl.

In an embodiment, R¹ is C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻² or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R¹⁻³; and the heteroatom in the 3-6 membered

heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1.

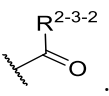
In an embodiment, R^{1-2} is each independently selected from cyano, or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} .

In an embodiment, R^{1-2-1} is each independently halogen.

In an embodiment, R^{1-3} is each independently C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} .

In an embodiment, R^{1-3-1} is each independently halogen.

In an embodiment, R^2 is hydrogen or 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in the 4-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2.

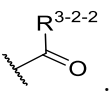
In an embodiment, R^{2-3} is each independently .

In an embodiment, R^{2-3-2} is C_1 - C_6 alkyl.

In an embodiment, R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{5-2} ; the heteroatom in the 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and the heteroatom in the 5-10 membered heterocycloalkyl is N, O and S, and the number of heteroatom(s) is 1 or 2.

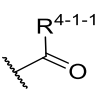
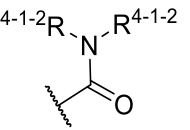
In an embodiment, R^{3-1} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{3-1-1} .

In an embodiment, R^{3-1-1} is each independently halogen.

In an embodiment, R^{3-2} is each independently .

In an embodiment, R^{3-2-2} is C_1 - C_6 alkyl or C_2 - C_4 alkenyl.

In an embodiment, R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; and the heteroatom in the 5-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1, 2 or 3.

In an embodiment, R^{4-1} is each independently  or .

In an embodiment, R^{4-1-1} is C_1 - C_6 alkyl.

In an embodiment, R^{4-1-2} is each independently C_1 - C_6 alkyl.

In an embodiment, R^1 is C_3 - C_6 cycloalkyl or 4 membered heterocycloalkyl, unsubstituted or substituted by one or more R^{1-2} ; and the heteroatom in the 4 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1.

In an embodiment, R^2 is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or

more R^{2-3} ; and the heteroatom in the 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2.

In an embodiment, R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 5-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1.

In an embodiment, R^{3-2-2} is C_2 - C_4 alkenyl.

In an embodiment, R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; and the heteroatom in the 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2.

In an embodiment, R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} .

In an embodiment, R^2 is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; and the heteroatom in the 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2.

In an embodiment, R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; and the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3.

In an embodiment, R^4 is 7-9 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; and the heteroatom in the 7-9 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1.

In an embodiment, R^1 is C_3 - C_6 cycloalkyl substituted by one or more R^{1-2} , or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; and the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3.

In an embodiment, R^{1-2} is each independently C_2 - C_6 alkynyl.

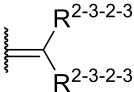
In an embodiment, R^{1-3} is each independently selected from cyano, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} , or C_2 - C_6 alkynyl.

In an embodiment, R^{1-3-1} is each independently halogen.

In an embodiment, R^2 is 4-12 membered heterocycloalkyl substituted by one or more R^{2-3} ; and the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O, and S, and the number of heteroatom(s) is 1, 2 or 3.

In an embodiment, R^{2-3} is each independently selected from , or 5-10 membered heteroaryl; and the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatoms is 2 or 3.

In an embodiment, R^{2-3-2} is C_1 - C_6 alkyl substituted by one or more $R^{2-3-2-1}$, C_3 - C_6 cycloalkyl unsubstituted or

substituted by one or more $R^{2-3-2-2}$, , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-5}$, or 5-10 membered heteroaryl; the heteroatom in the 3-6 membered

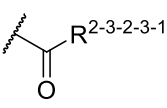
heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2.

In an embodiment, $R^{2-3-2-1}$ is each independently selected from hydroxyl or  $R^{2-3-2-1-1}$.

In an embodiment, $R^{2-3-2-1-1}$ is each independently C_1 - C_6 alkyl.

In an embodiment, $R^{2-3-2-2}$ is each independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$, or amino.

In an embodiment, $R^{2-3-2-2-2}$ is each independently deuterium.

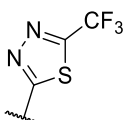
In an embodiment, $R^{2-3-2-3}$ is each independently selected from halogen or  $R^{2-3-2-3-1}$.

In an embodiment, $R^{2-3-2-3-1}$ is each independently 6-10 membered aryl unsubstituted or substituted by one or more $R^{2-3-2-3-1-1}$; and $R^{2-3-2-3-1-1}$ is each independently C_1 - C_6 alkoxy.

In an embodiment, $R^{2-3-2-5}$ is each independently selected from halogen, C_1 - C_6 alkoxy, or C_1 - C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-5-1}$.

In an embodiment, R^{2-2-1} is each independently halogen.

In an embodiment, R^3 is unsubstituted 5-6 membered heteroaryl; and the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3.

In an embodiment, R^3 is .

In an embodiment, R^4 is deuterium, cyano, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} s; and the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O, and S, and the number of heteroatom(s) is 1 or 2.

In an embodiment, R^{4-1} is each independently ; and R^{4-1-1} is C_1 - C_6 alkyl.

In an embodiment, R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} ;

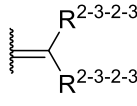
R^{1-2} is each independently selected from cyano, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} , or C_2 - C_6 alkynyl;

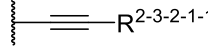
R^{1-2-1} is each independently selected from deuterium, halogen, or hydroxyl;

R^2 is 4-10 membered heterocycloalkyl substituted by one or more R^{2-3} ; the heteroatom in the 4-10 membered heterocycloalkyl is N and/or O, and the number of heteroatom(s) is 1, 2 or 3; the 4-10 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring, a 7-10 membered saturated spiro ring or a 7-10 membered saturated bridged ring;

R^{2-3} is each independently selected from , or 5-10 membered heteroaryl; the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatoms is 2 or 3;

R^{2-3-2} is C_1 - C_6 alkyl substituted by one or more $R^{2-3-2-1}$, C_3 - C_6 cycloalkyl unsubstituted or substituted by one

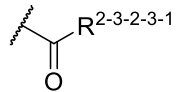
or more $R^{2-3-2-2}$, , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-5}$, or 5-10 membered heteroaryl; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring; the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

$R^{2-3-2-1}$ is each independently selected from hydroxyl, or , ;

$R^{2-3-2-1-1}$ is each independently C_1 - C_6 alkyl;

$R^{2-3-2-2}$ is each independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$, or amino;

$R^{2-3-2-2-2}$ is each independently deuterium;

$R^{2-3-2-3}$ is each independently selected from hydrogen or , ;

$R^{2-3-2-3-1}$ is each independently 6-10 membered aryl unsubstituted or substituted by one or more $R^{2-3-2-3-1-1}$;

$R^{2-3-2-3-1-1}$ is each independently C_1 - C_6 alkoxy;

$R^{2-3-2-5}$ is each independently selected from halogen, C_1 - C_6 alkoxy, or C_1 - C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-5-1}$;

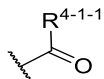
$R^{2-3-2-5-1}$ is each independently halogen;

R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R^{3-1} is each independently C_1 - C_6 alkyl substituted by one or more R^{3-1-1} ;

R^{3-1-1} is each independently halogen;

R^4 is hydrogen, cyano, halogen, C_1 - C_6 alkyl, or 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1 or 2; the 5-10 membered heterocycloalkyl is a 7-10 membered unsaturated spiro ring;

R^{4-1} is each independently , ; and R^{4-1-1} is C_1 - C_6 alkyl.

In an embodiment, R¹ is C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻²;

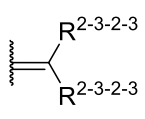
R¹⁻² is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻²⁻¹, or C₂-C₆ alkynyl;

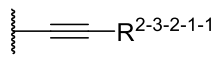
R¹⁻²⁻¹ is each independently selected from deuterium, halogen, or hydroxyl;

R² is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in the 4-10 membered heterocycloalkyl is N and/or O, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³ is each independently selected from , or 5-10 membered heteroaryl; the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatoms is 2 or 3;

R²⁻³⁻² is C₁-C₆ alkyl substituted by one or more R²⁻³⁻²⁻¹, C₃-C₆ cycloalkyl unsubstituted or substituted by one

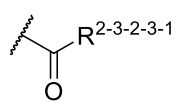
or more R²⁻³⁻²⁻², , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻⁵, or 5-10 membered heteroaryl; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

R²⁻³⁻²⁻¹ is each independently selected from hydroxyl, or  ;

R²⁻³⁻²⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R²⁻³⁻²⁻² is each independently selected from halogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻², or amino;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻²⁻³ is each independently selected from hydrogen or  ;

R²⁻³⁻²⁻³⁻¹ is each independently 6-10 membered aryl unsubstituted or substituted by one or more R²⁻³⁻²⁻³⁻¹⁻¹;

R²⁻³⁻²⁻³⁻¹⁻¹ is each independently C₁-C₆ alkoxy;

R²⁻³⁻²⁻⁵ is each independently selected from halogen, C₁-C₆ alkoxy, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻⁵⁻¹;

R²⁻³⁻²⁻⁵⁻¹ is each independently halogen;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R⁴ is hydrogen, cyano, halogen, C₁-C₆ alkyl, or 5-10 membered heterocycloalkyl unsubstituted or substituted

by one or more R^{4-1} ; the heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1 or 2;

R^{4-1} is each independently ; and R^{4-1-1} is C_1 - C_6 alkyl.

In an embodiment, R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} ;

R^{1-2} is each independently selected from cyano, or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} ;

R^{1-2-1} is each independently selected from deuterium or halogen;

R^2 is 4-10 membered heterocycloalkyl substituted by one or more R^{2-3} ; the heteroatom in the 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1, 2 or 3; the 4-10 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring or a 7-10 membered saturated spiro ring;

R^{2-3} is each independently ;

R^{2-3-2} is C_3 - C_6 cycloalkyl substituted by one or more $R^{2-3-2-2}$, 3-6 membered heterocycloalkyl substituted by one or more $R^{2-3-2-5}$; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring; the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

$R^{2-3-2-2}$ is each independently selected from C_1 - C_6 alkyl, or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$;

$R^{2-3-2-2-2}$ is each independently deuterium;

$R^{2-3-2-5}$ is each independently C_1 - C_6 alkyl;

R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R^{3-1} is each independently C_1 - C_6 alkyl substituted by one or more R^{3-1-1} ;

R^{3-1-1} is each independently halogen;

R^4 is hydrogen, cyano, or C_1 - C_6 alkyl.

In an embodiment, R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} ;

R^{1-2} is each independently selected from cyano, or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} ;

R^{1-2-1} is each independently selected from deuterium or halogen;

R^2 is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in the 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3} is each independently  ;

R^{2-3-2} is C_3-C_6 cycloalkyl substituted by one or more $R^{2-3-2-2}$, or 3-6 membered heterocycloalkyl substituted by one or more $R^{2-3-2-5}$; the heteroatom in the 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in the 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

$R^{2-3-2-2}$ is each independently selected from C_1-C_6 alkyl, or C_1-C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$;

$R^{2-3-2-2-2}$ is each independently deuterium;

$R^{2-3-2-5}$ is each independently C_1-C_6 alkyl;

R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R^{3-1} is each independently C_1-C_6 alkyl substituted by one or more R^{3-1-1} ;

R^{3-1-1} is each independently halogen;

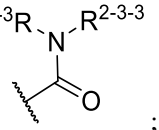
R^4 is hydrogen, cyano, or C_1-C_6 alkyl.

In an embodiment, R^1 is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in the 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1; the 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring;

R^{1-3} is each independently selected from cyano, C_1-C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} , or C_2-C_6 alkynyl;

R^{1-3-1} is each independently selected from halogen or deuterium;

R^2 is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the 4-12 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring, a 7-10 membered saturated fused ring or a 7-10 membered saturated spiro ring;

R^{2-3} is each independently C_1-C_6 alkyl unsubstituted or substituted by one or more R^{2-3-1} ,  , or  ;

R^{2-3-1} is each independently selected from hydroxyl, halogen, C_1-C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-1-1}$, or amino unsubstituted or substituted by one or more $R^{2-3-1-3}$;

$R^{2-3-1-1}$ is each independently deuterium;

$R^{2-3-1-3}$ is each independently C_1-C_6 alkyl;

R^{2-3-2} is C_1-C_6 alkyl, or C_3-C_6 cycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-2}$;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

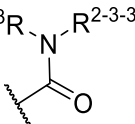
R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl.

In an embodiment, R¹ is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R¹⁻³; the heteroatom in the 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1;

R¹⁻³ is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹, or C₂-C₆ alkynyl;

R¹⁻³⁻¹ is each independently selected from halogen or deuterium;

R² is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O, and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³ is each independently C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻¹, , or  ;

R²⁻³⁻¹ is each independently selected from hydroxyl, halogen, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹, or amino unsubstituted or substituted by one or more R²⁻³⁻¹⁻³;

R²⁻³⁻¹⁻¹ is each independently deuterium;

R²⁻³⁻¹⁻³ is each independently C₁-C₆ alkyl;

R²⁻³⁻² is C₁-C₆ alkyl, or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻²;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

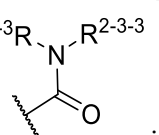
R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl.

In a preferred embodiment, R¹ is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R¹⁻³; the heteroatom in the 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1; the 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring;

R¹⁻³ is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹, or C₂-C₆ alkynyl;

R¹⁻³⁻¹ is each independently halogen;

R² is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the 4-12 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring, a 7-10 membered saturated fused ring or a 7-10 membered saturated spiro ring;

R²⁻³ is each independently C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻¹, , or  ;

R²⁻³⁻¹ is each independently selected from hydroxyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹;

R²⁻³⁻¹⁻¹ is each independently deuterium;

R²⁻³⁻² is C₁-C₆ alkyl, or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻²;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

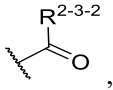
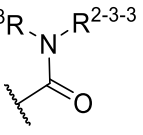
R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl.

In a preferred embodiment, R¹ is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R¹⁻³; the heteroatom in the 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1;

R¹⁻³ is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹, or C₂-C₆ alkynyl;

R¹⁻³⁻¹ is each independently halogen;

R² is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in the 4-12 membered heterocycloalkyl is one or more selected from N, O, and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³ is each independently C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻¹, , or  ;

R²⁻³⁻¹ is each independently selected from hydroxyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹;

R²⁻³⁻¹⁻¹ is each independently deuterium;

R²⁻³⁻² is C₁-C₆ alkyl, or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻²;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

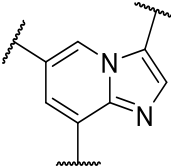
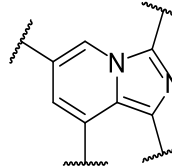
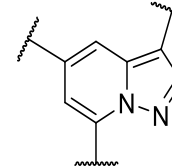
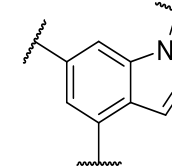
R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in the 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

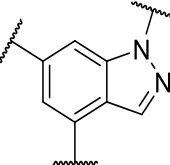
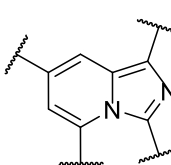
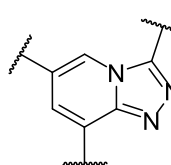
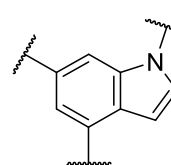
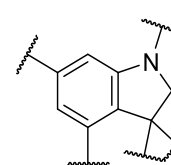
R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

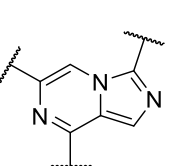
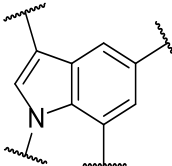
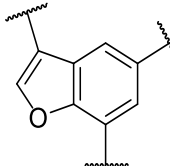
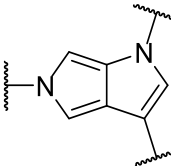
R³⁻¹⁻¹ is each independently halogen;

R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl.

In an embodiment, ring B is

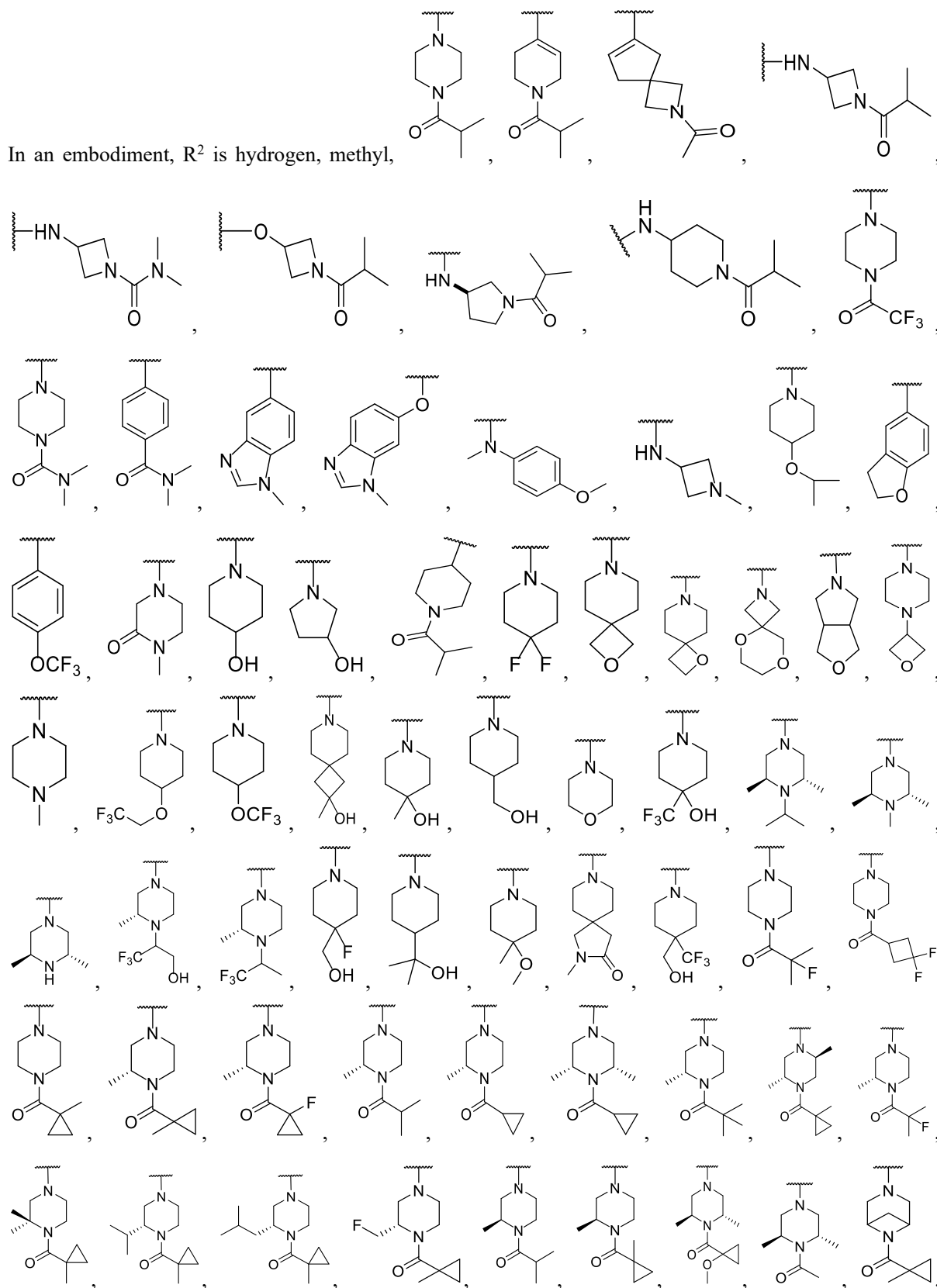
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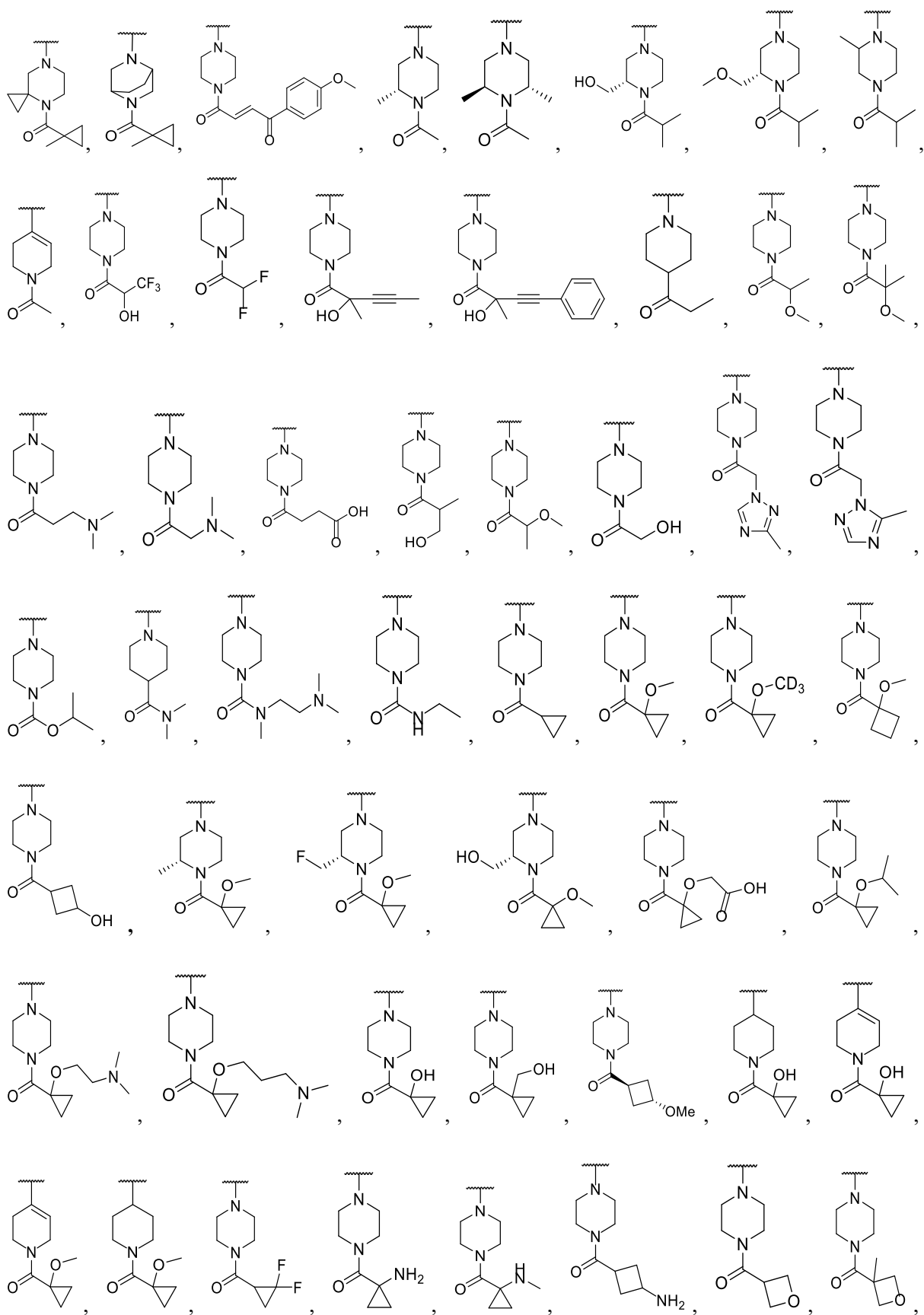
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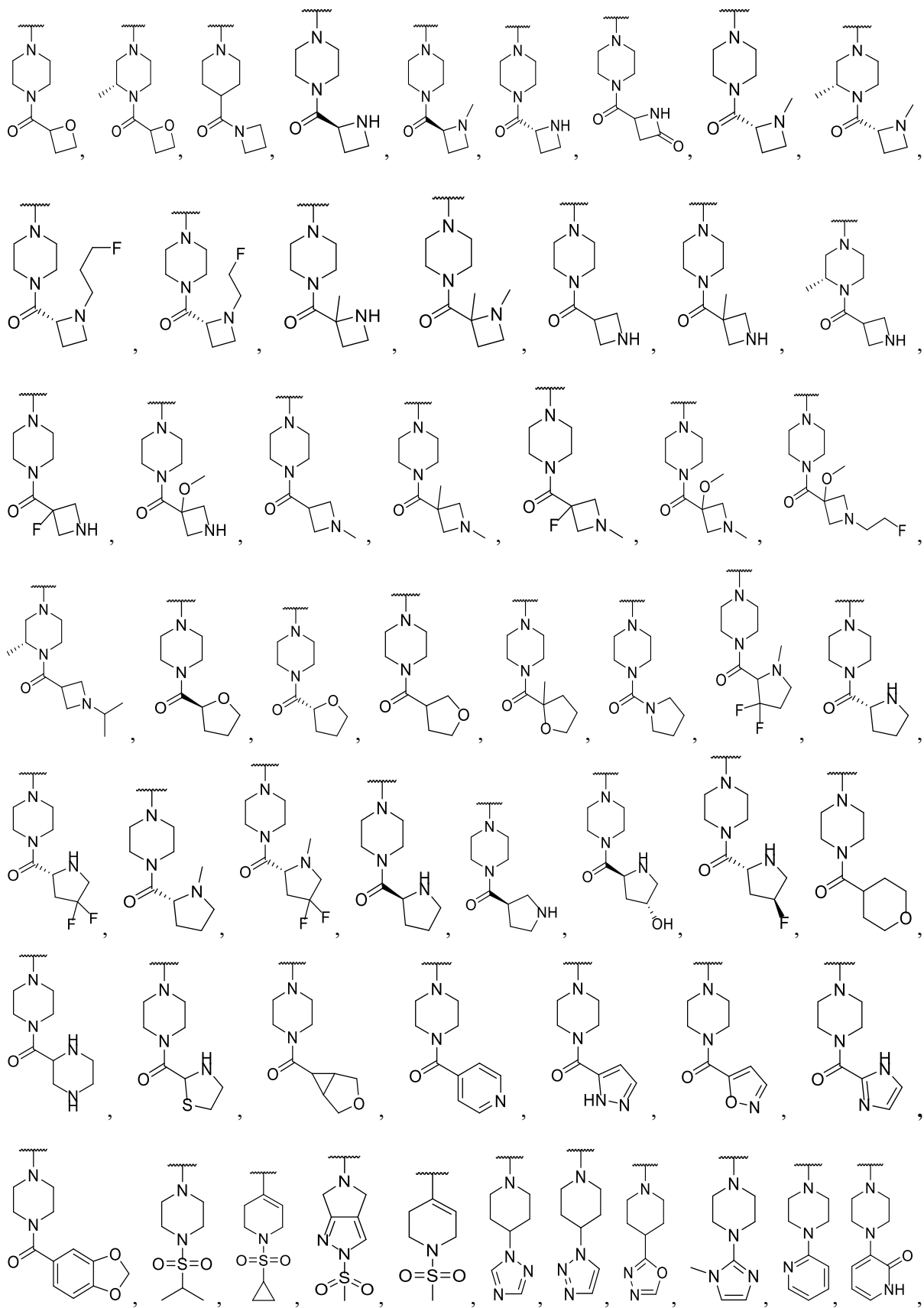
 ,  ,  or .

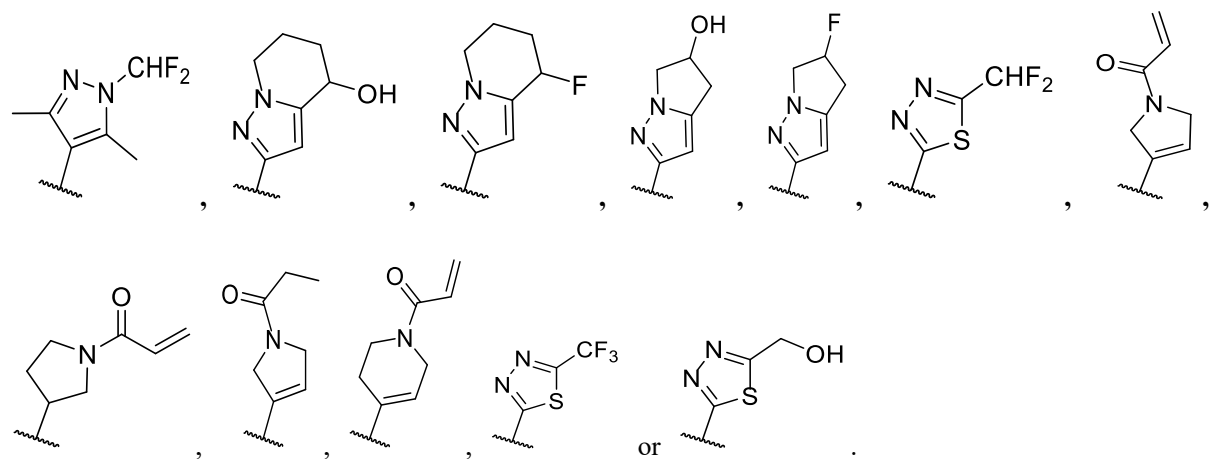
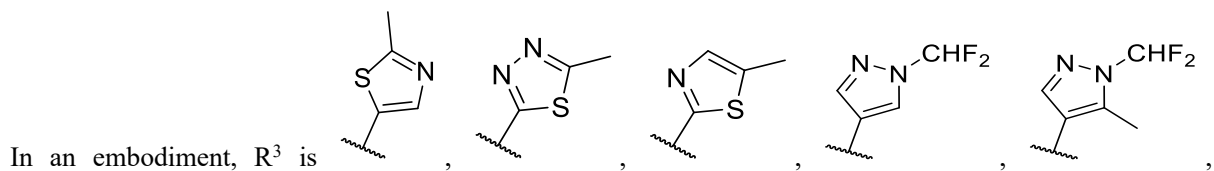
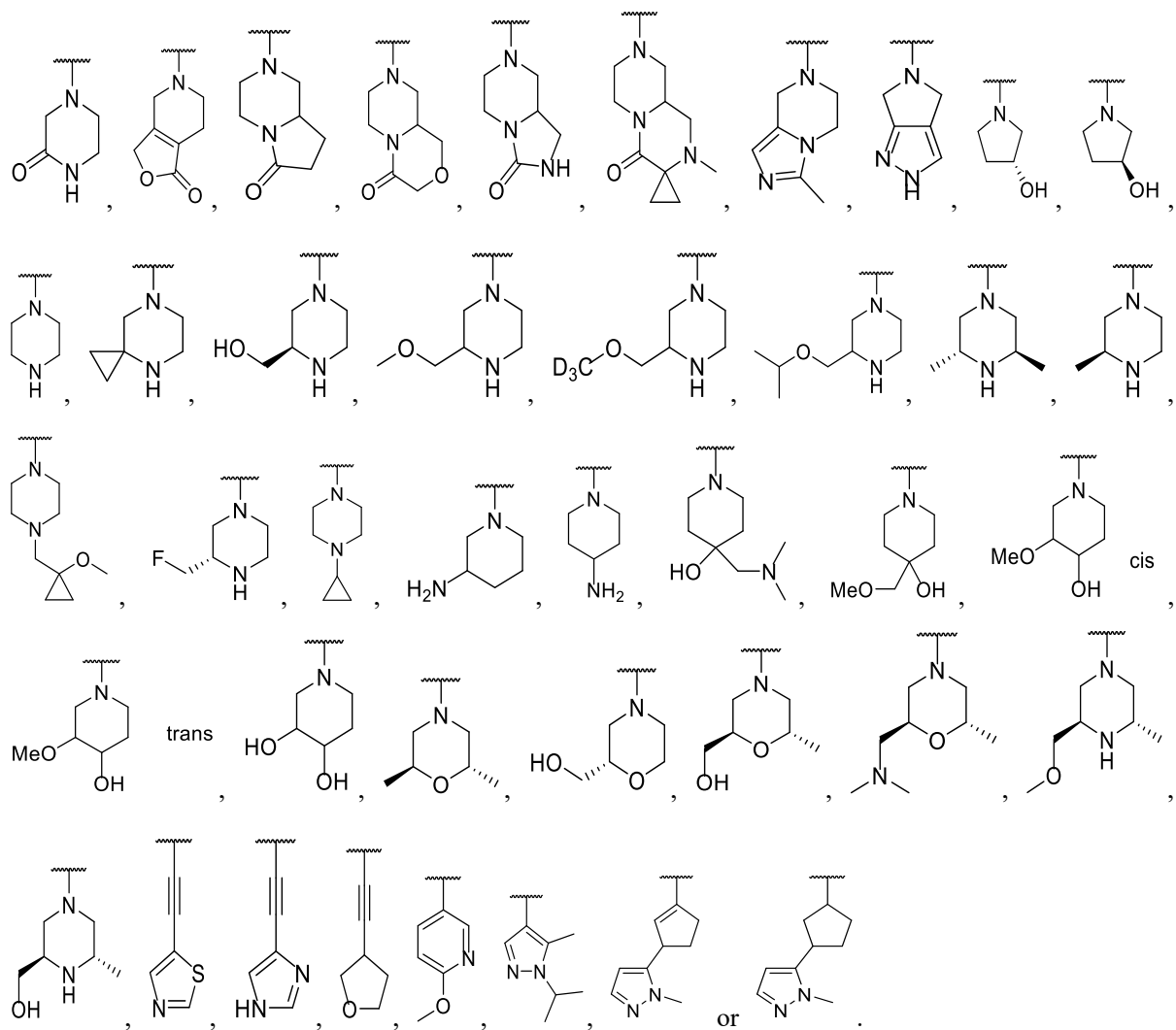
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In an embodiment, R² is hydrogen, methyl,

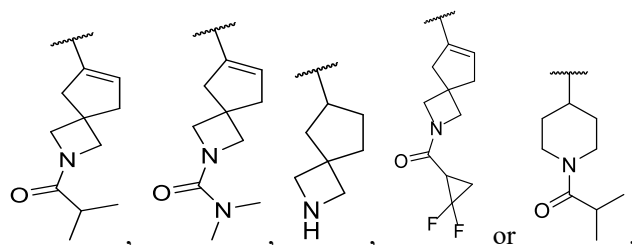
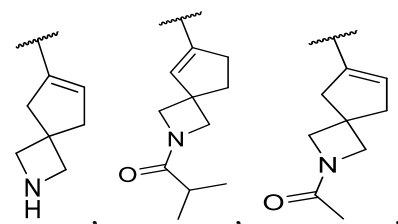




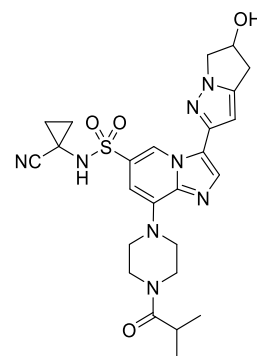
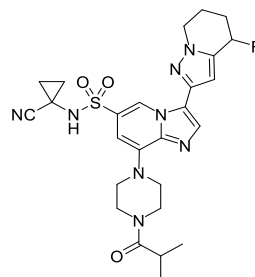
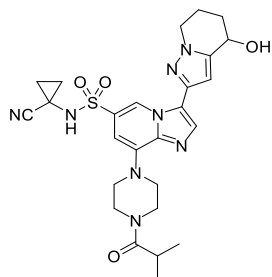
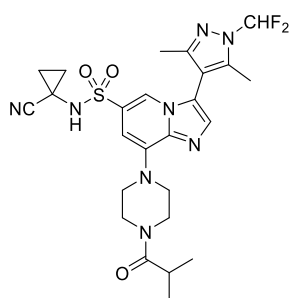
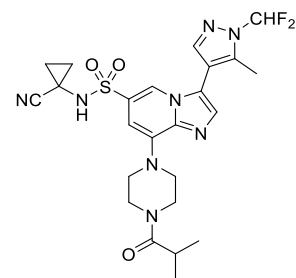
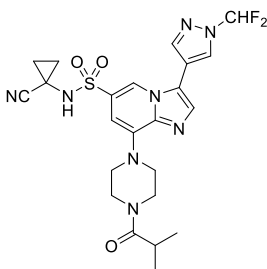
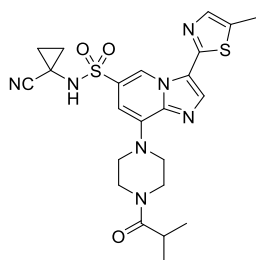
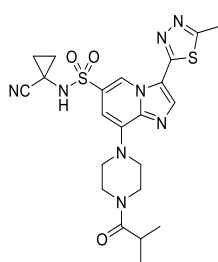
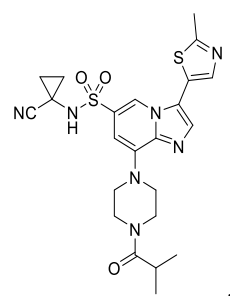


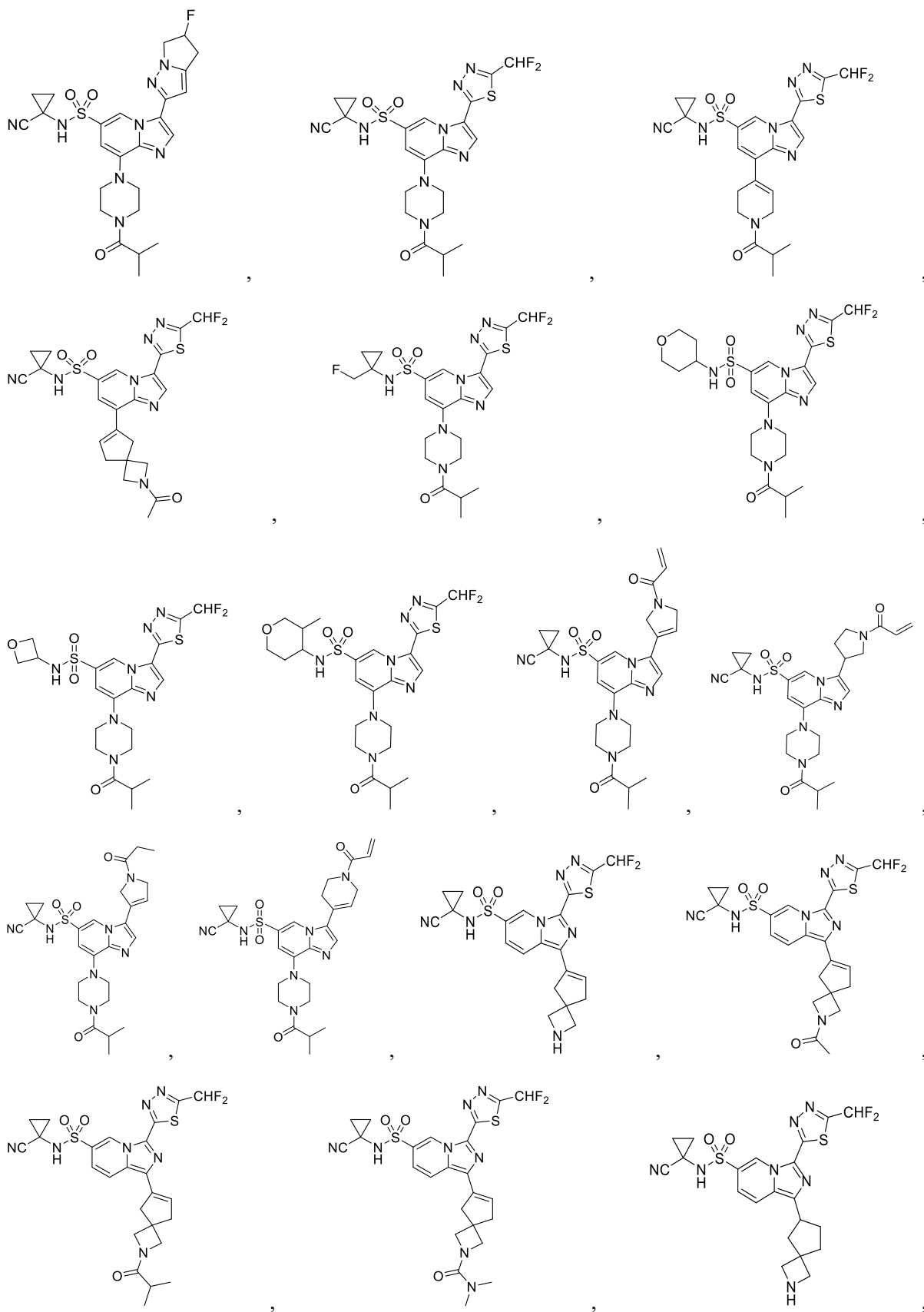


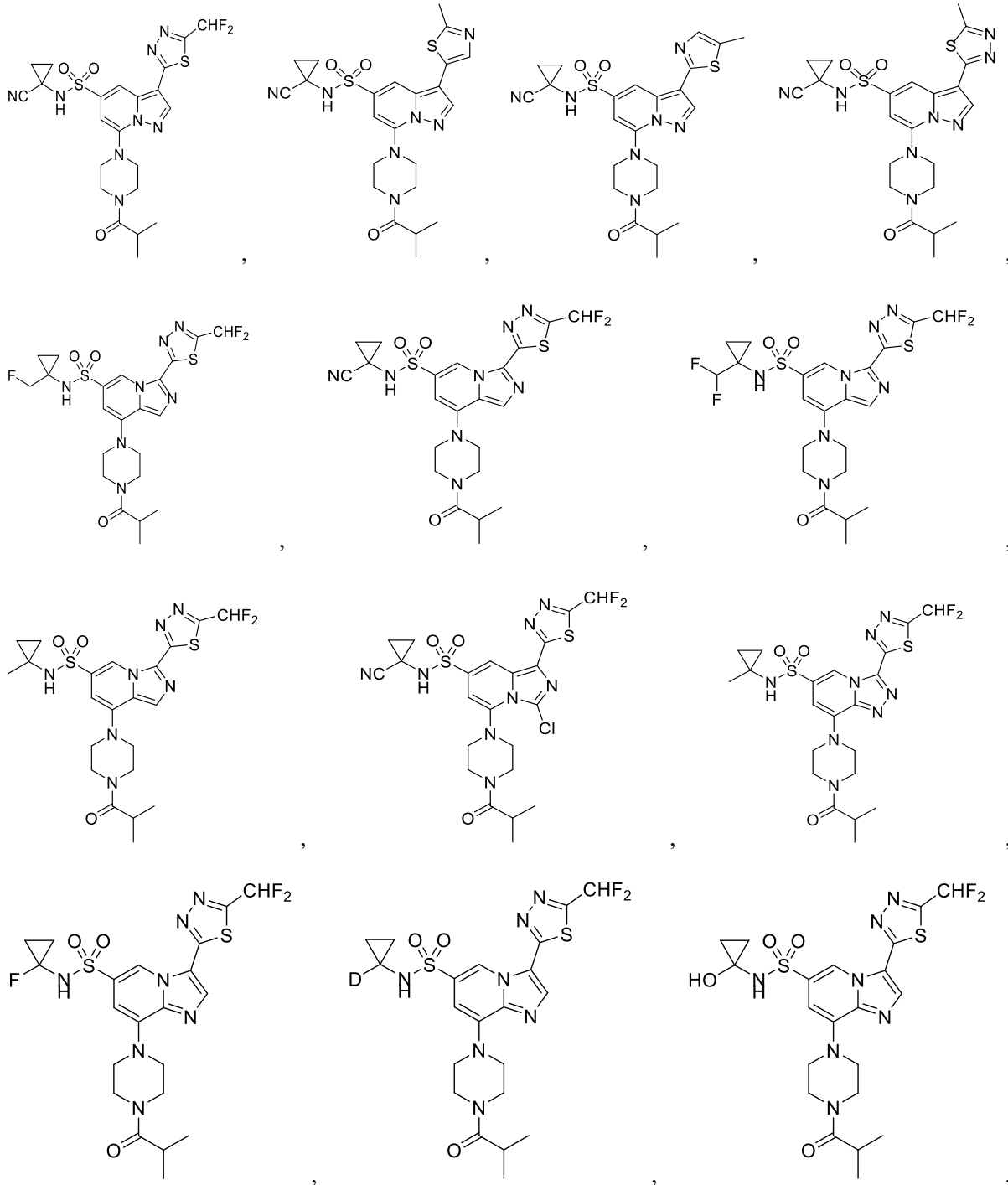
In an embodiment, R⁴ is hydrogen, deuterium, Cl, F, CN, methyl,

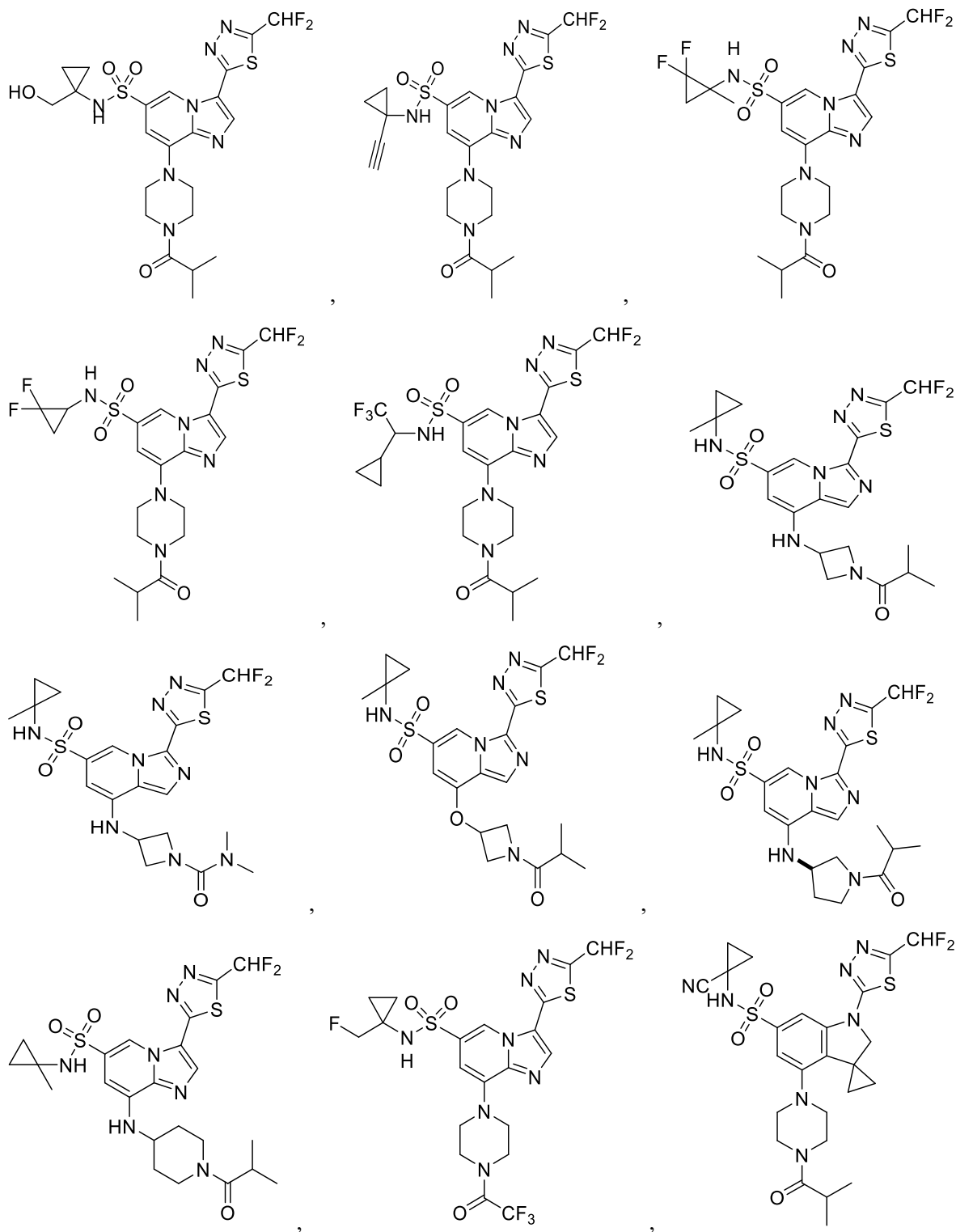


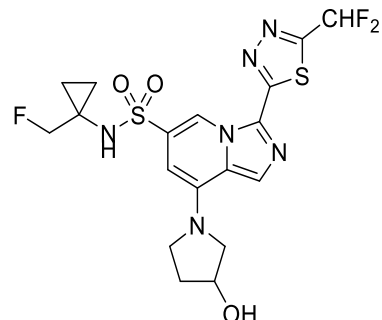
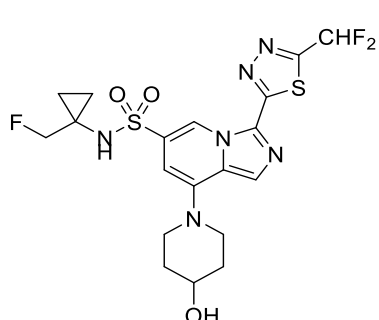
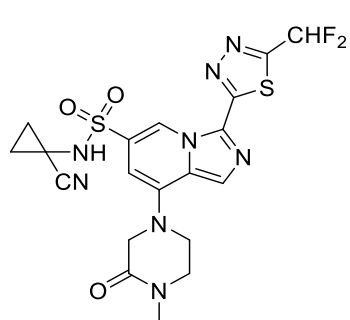
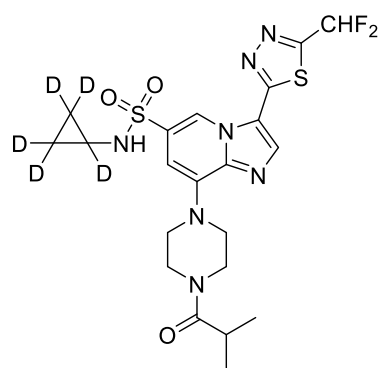
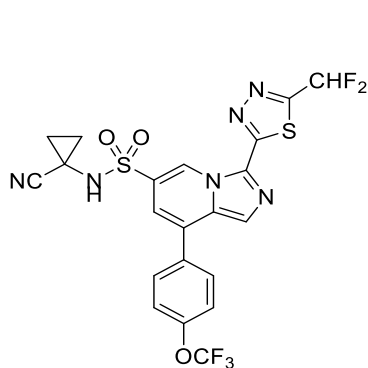
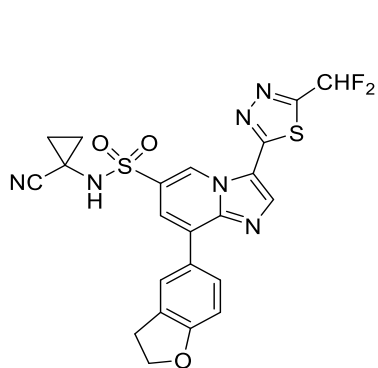
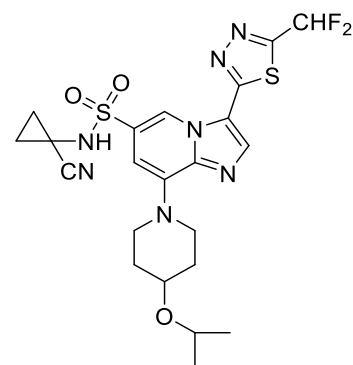
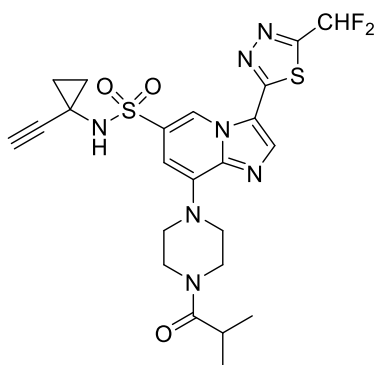
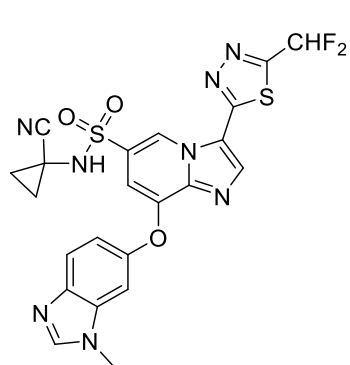
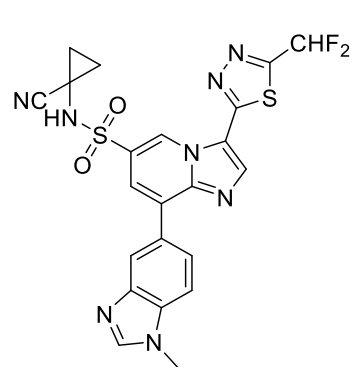
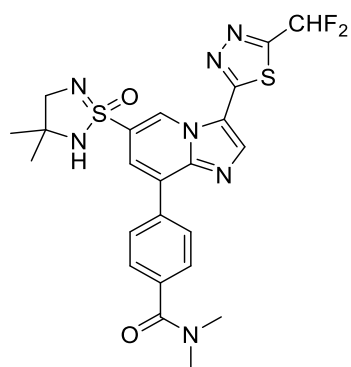
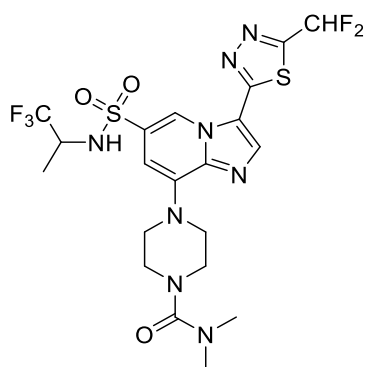
In an embodiment, the compound of formula I is any one of the following compounds:

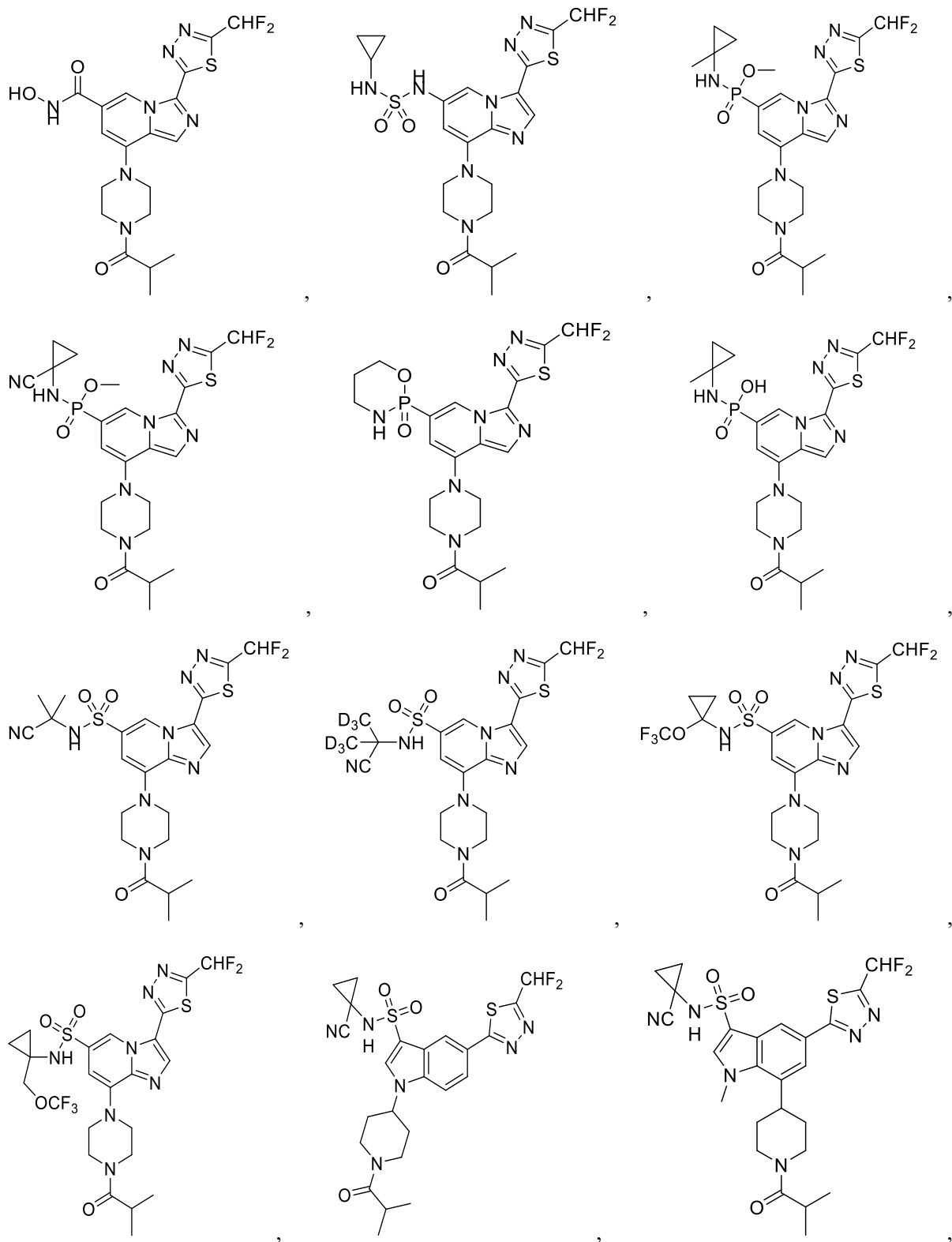


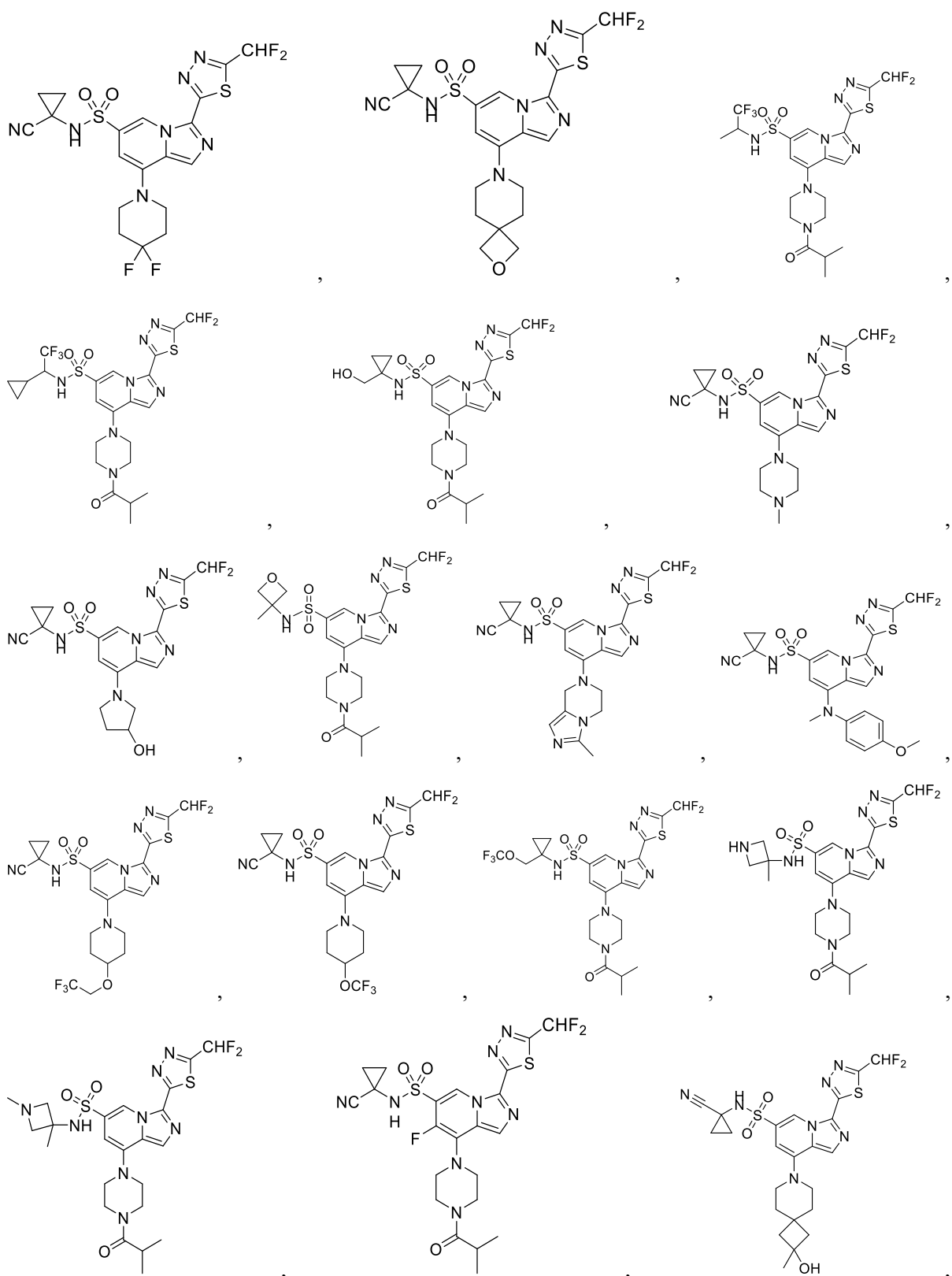


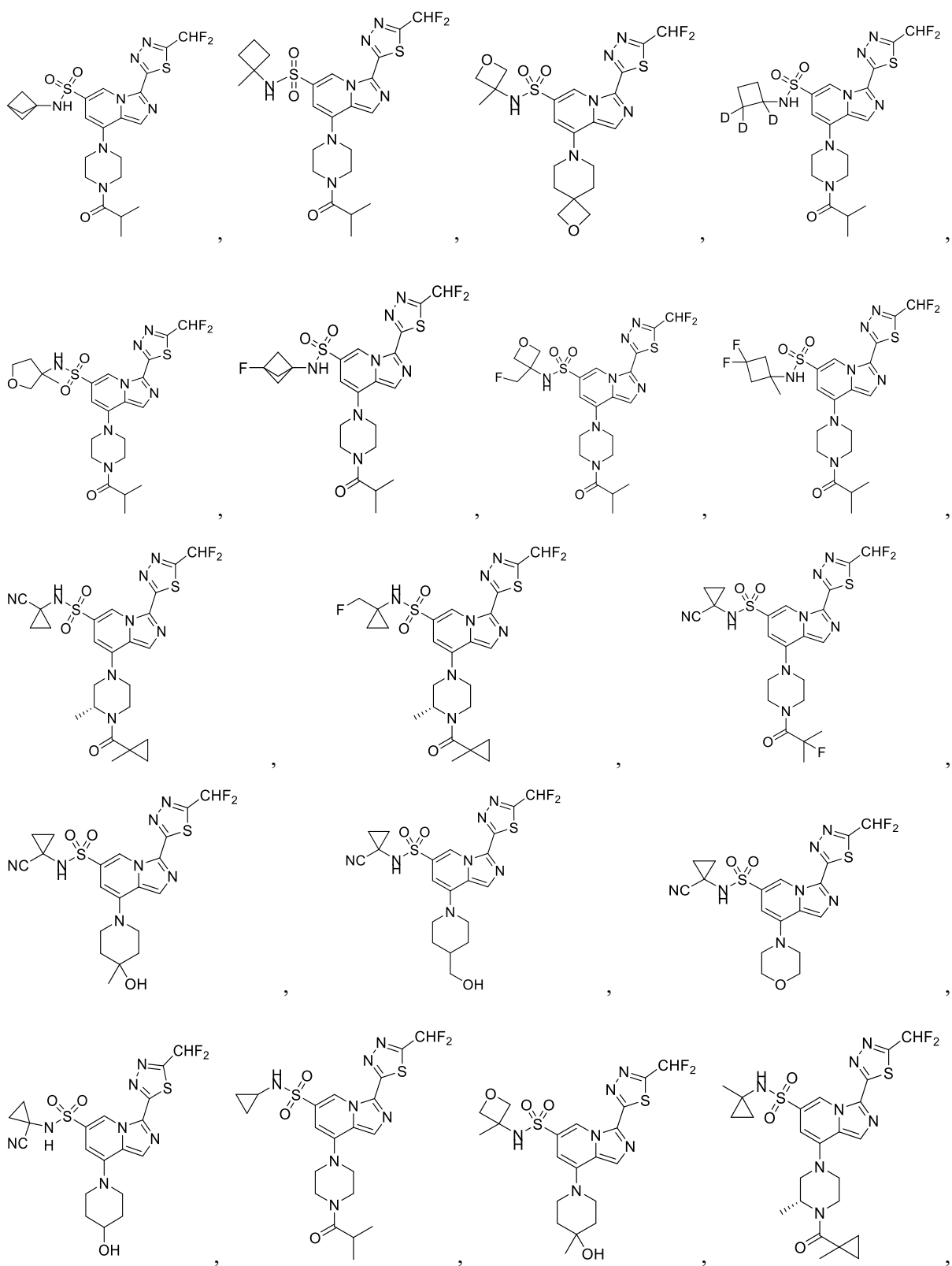


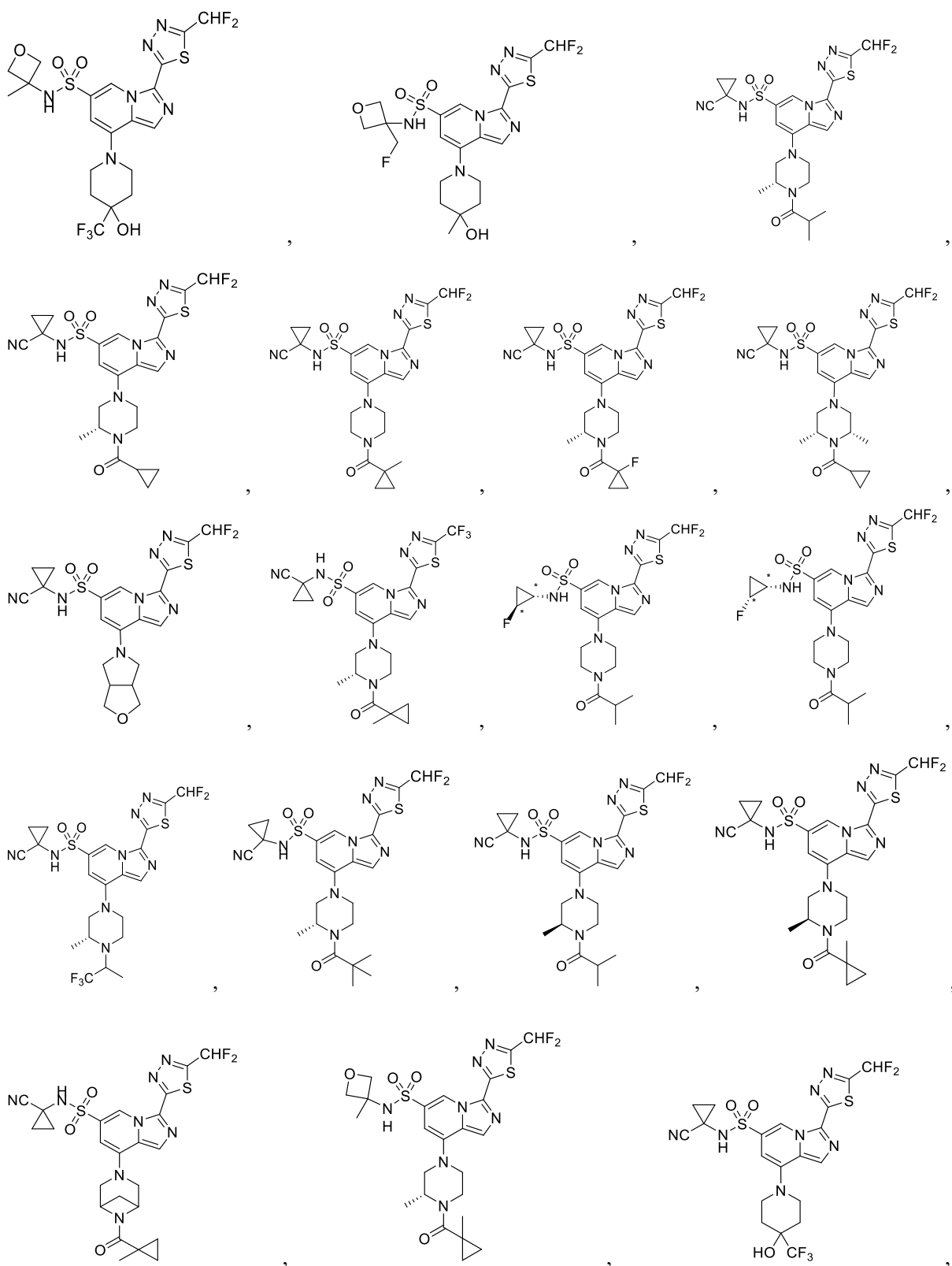


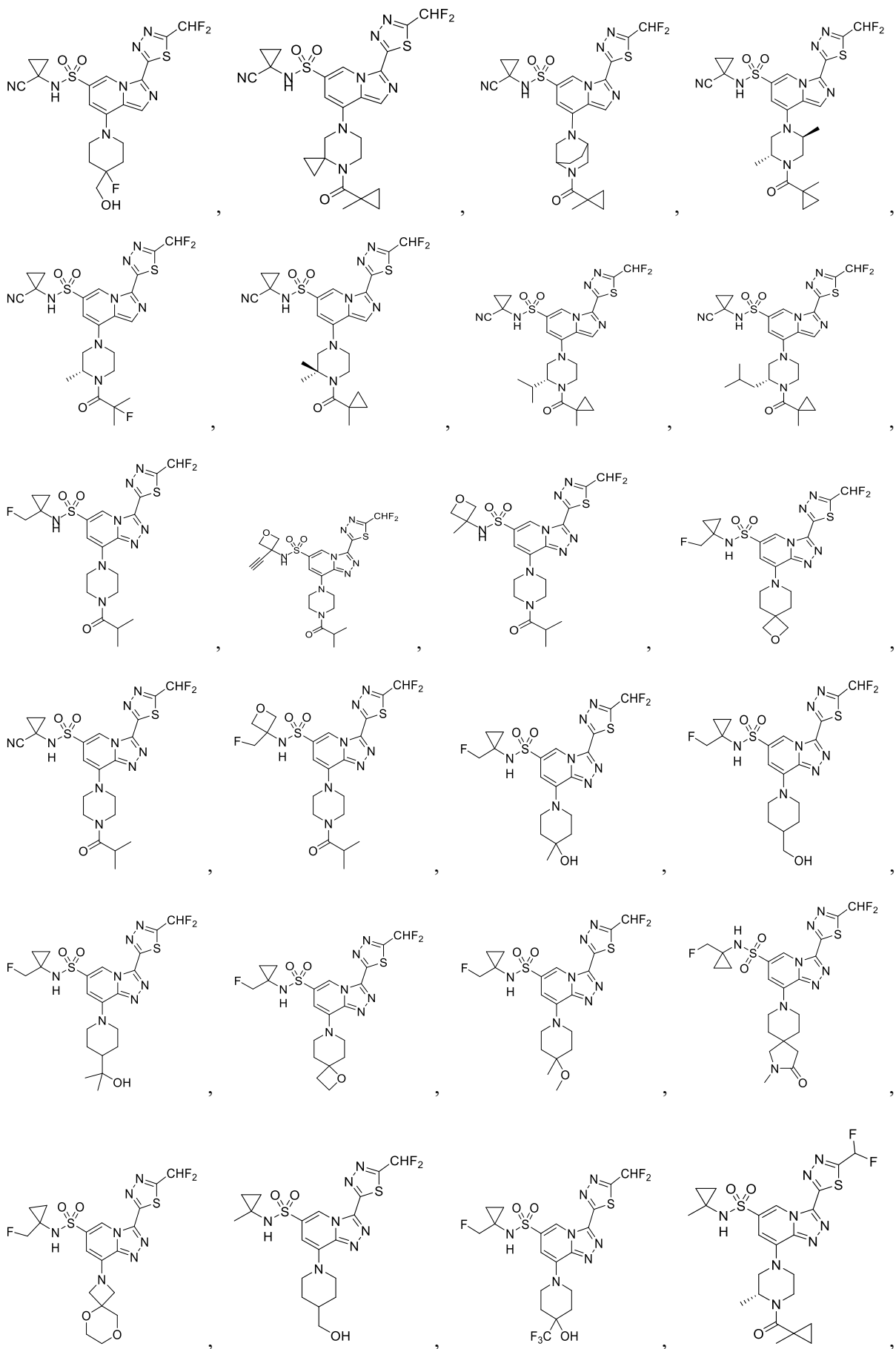


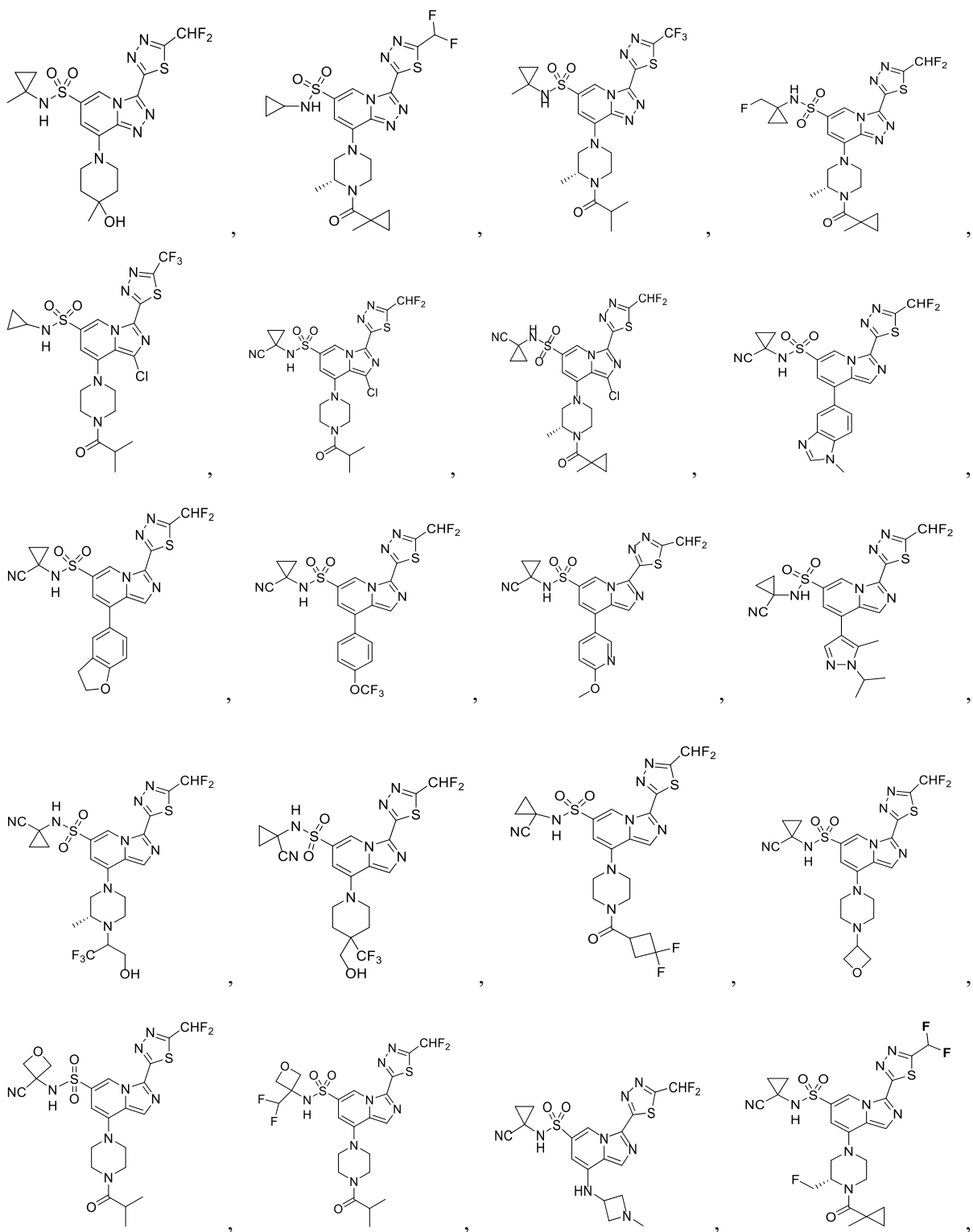


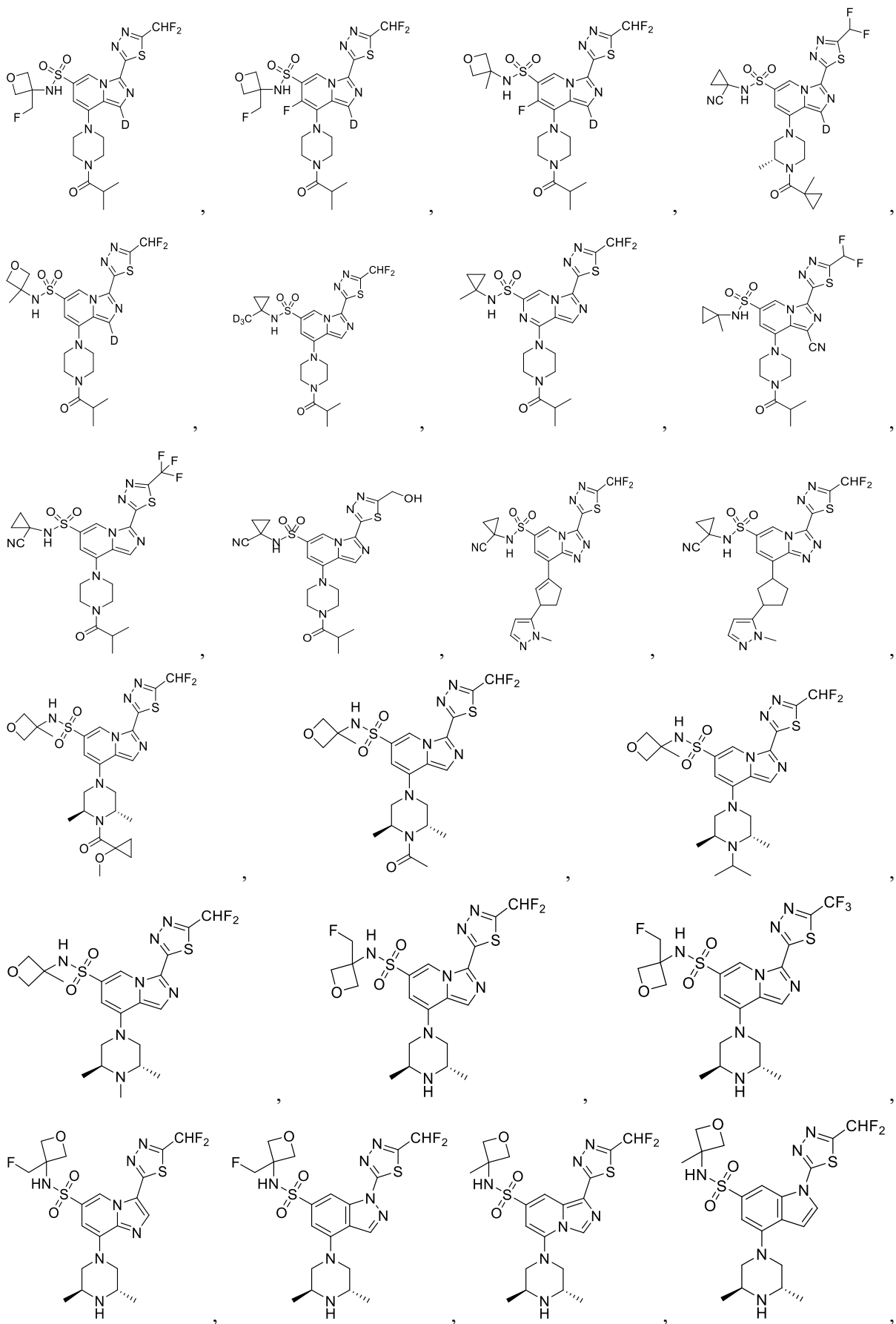




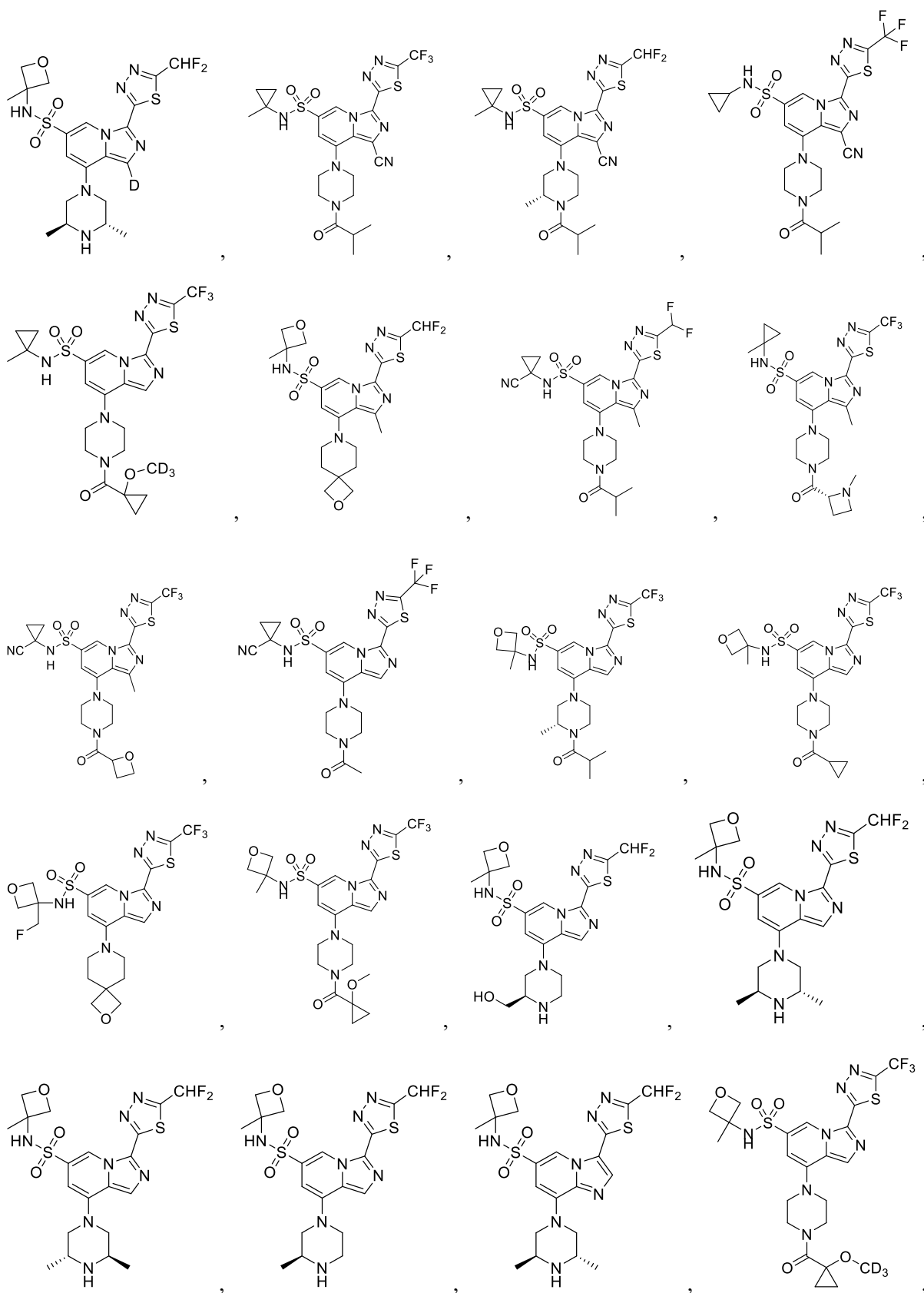


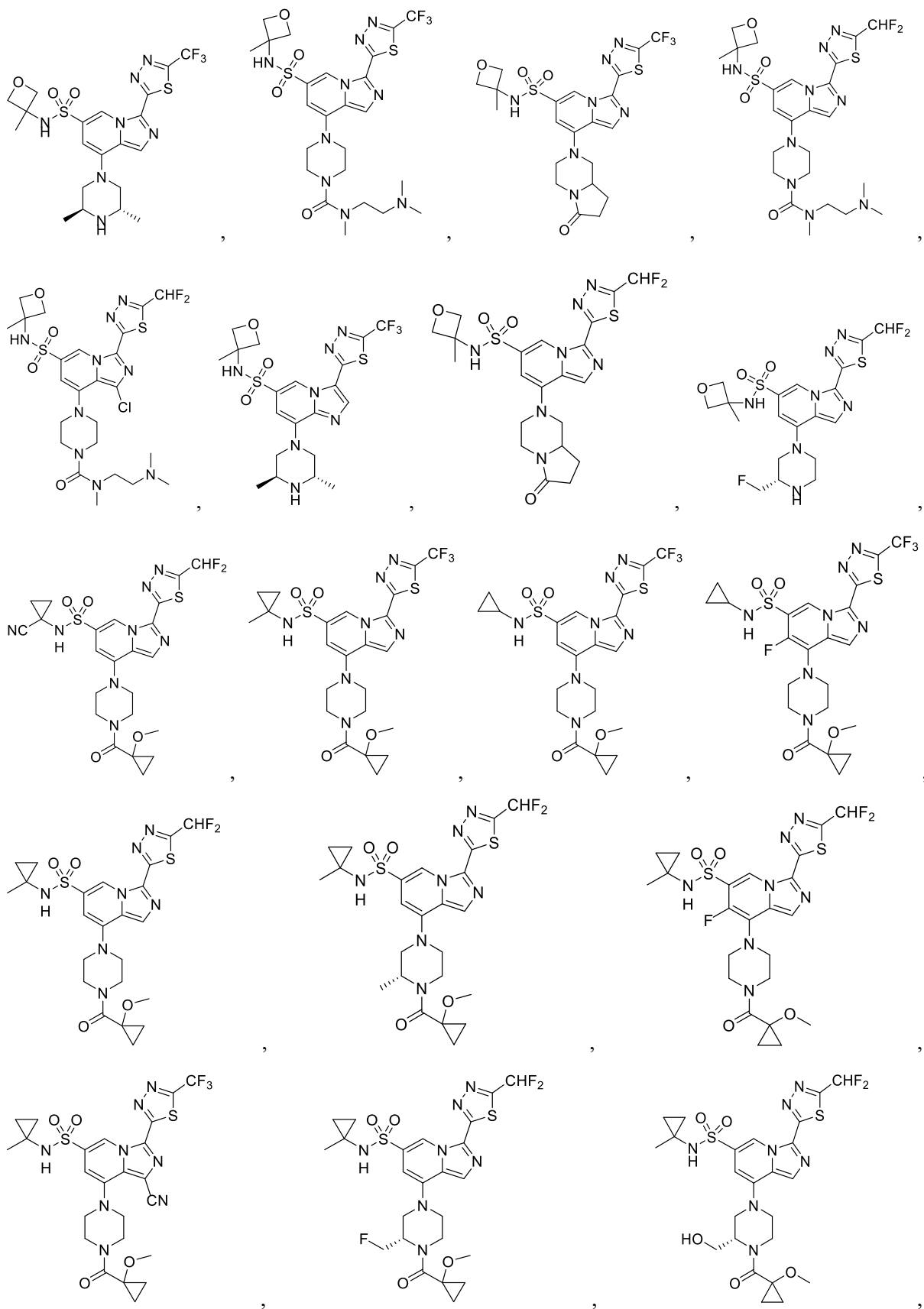


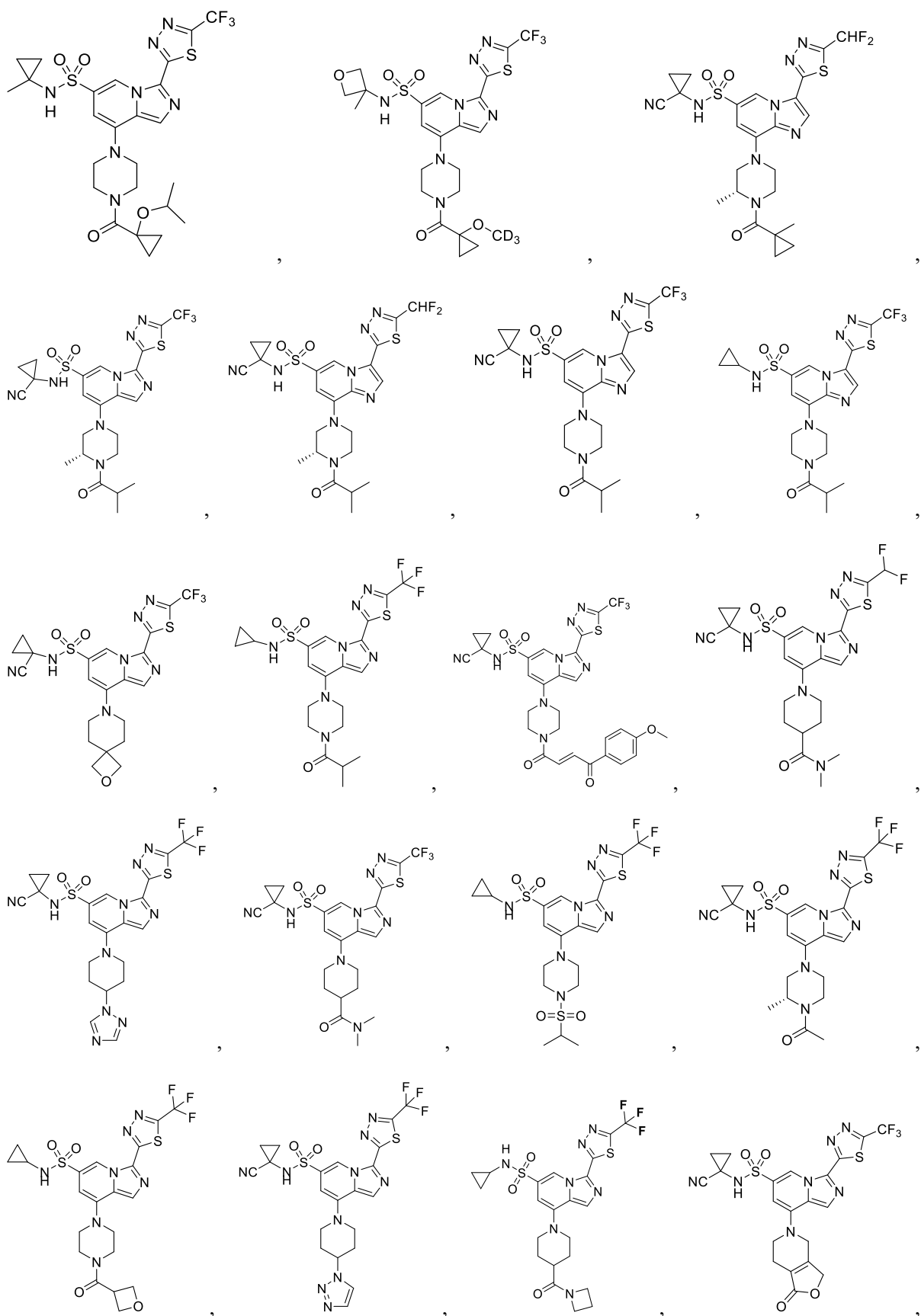


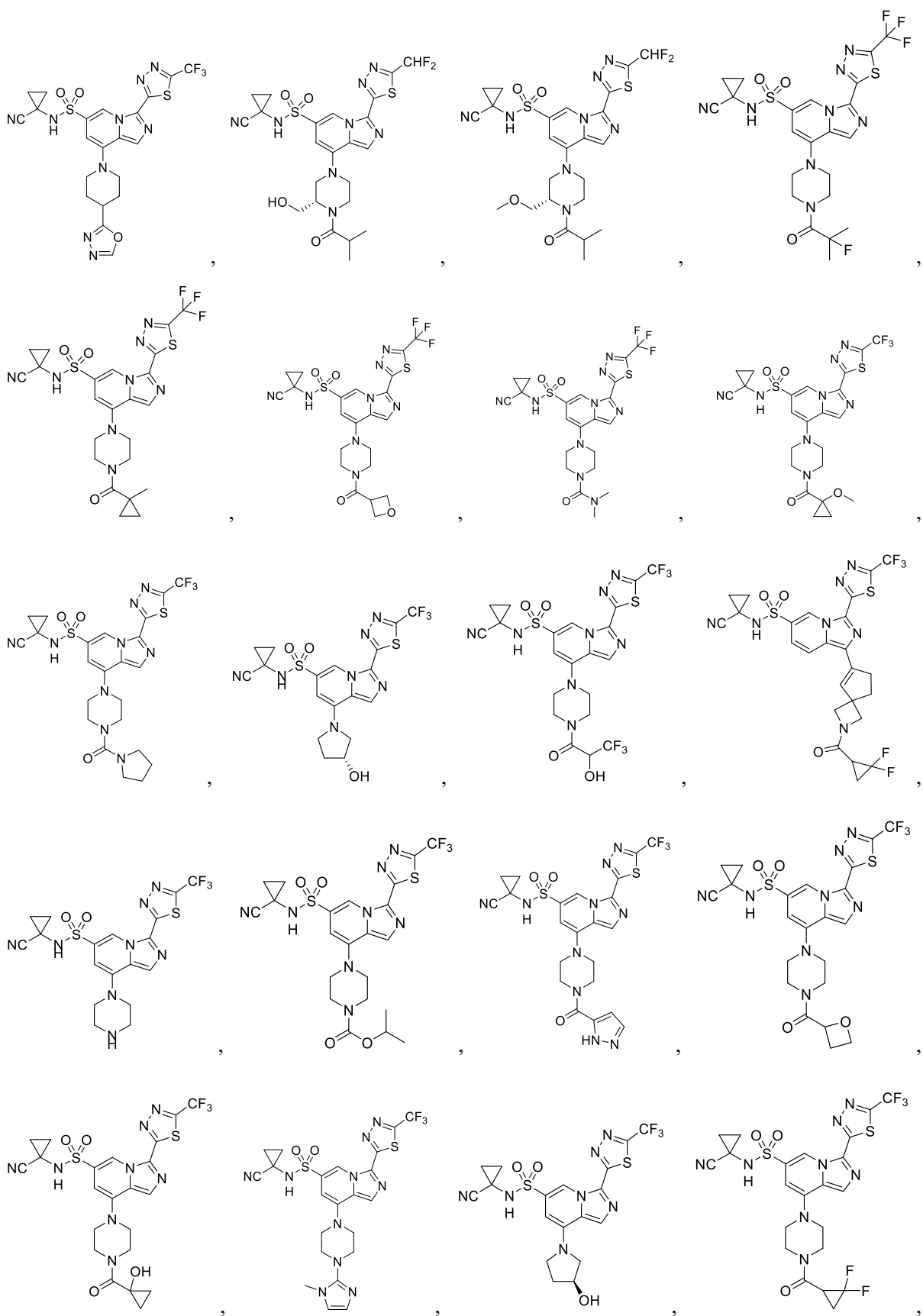


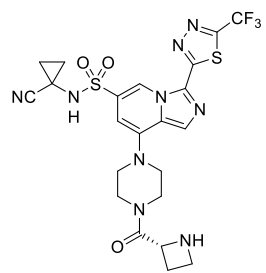
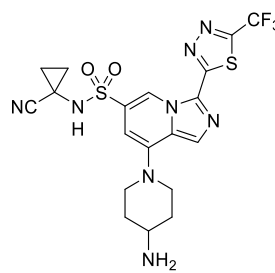
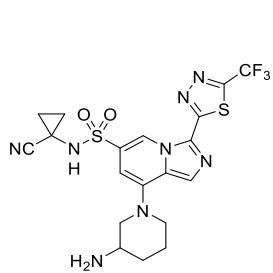
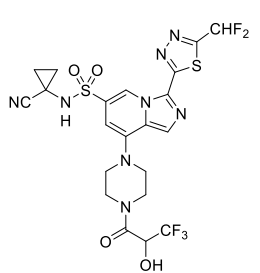
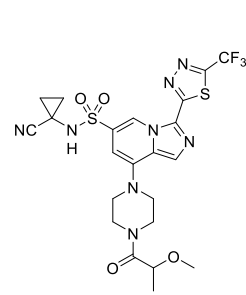
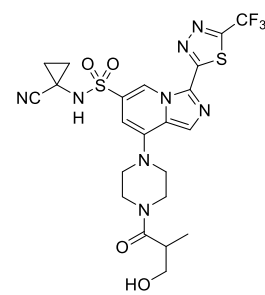
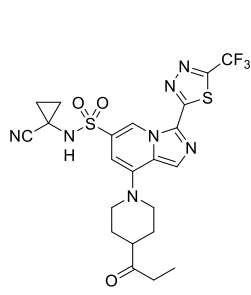
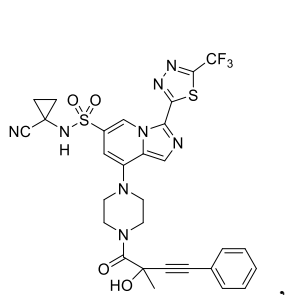
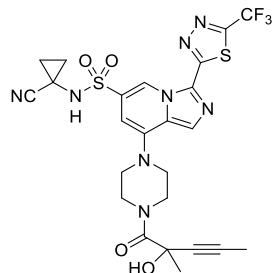
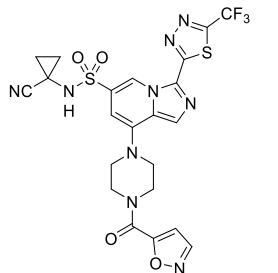
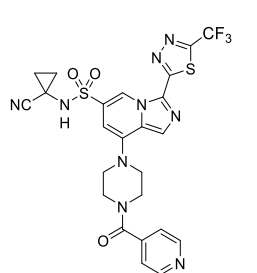
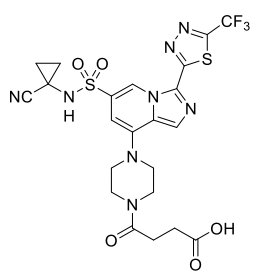
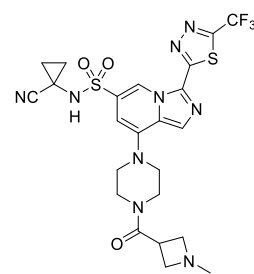
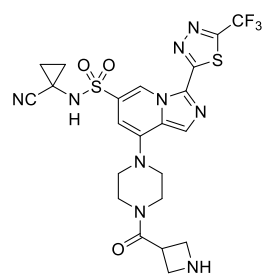
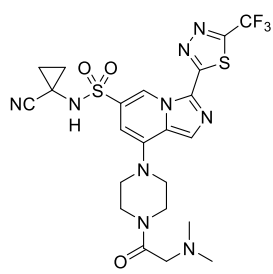
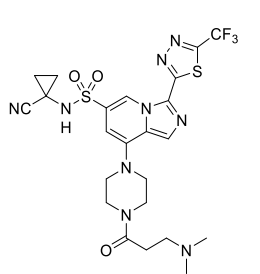
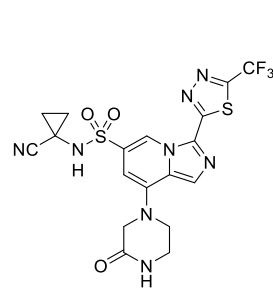
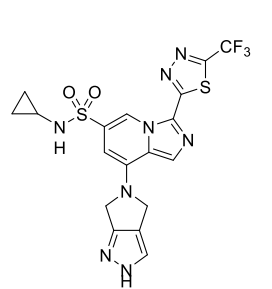
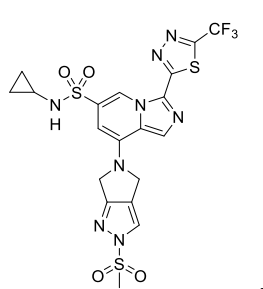
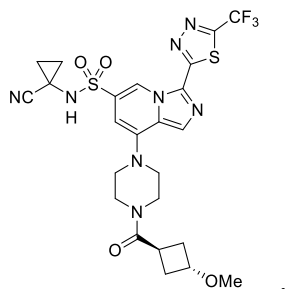
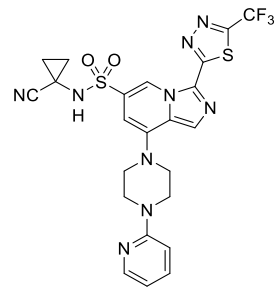
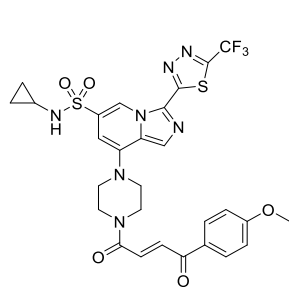
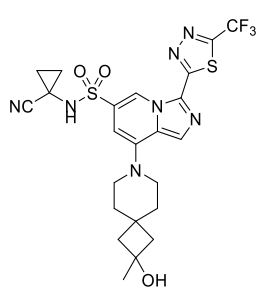
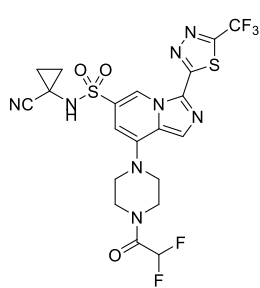


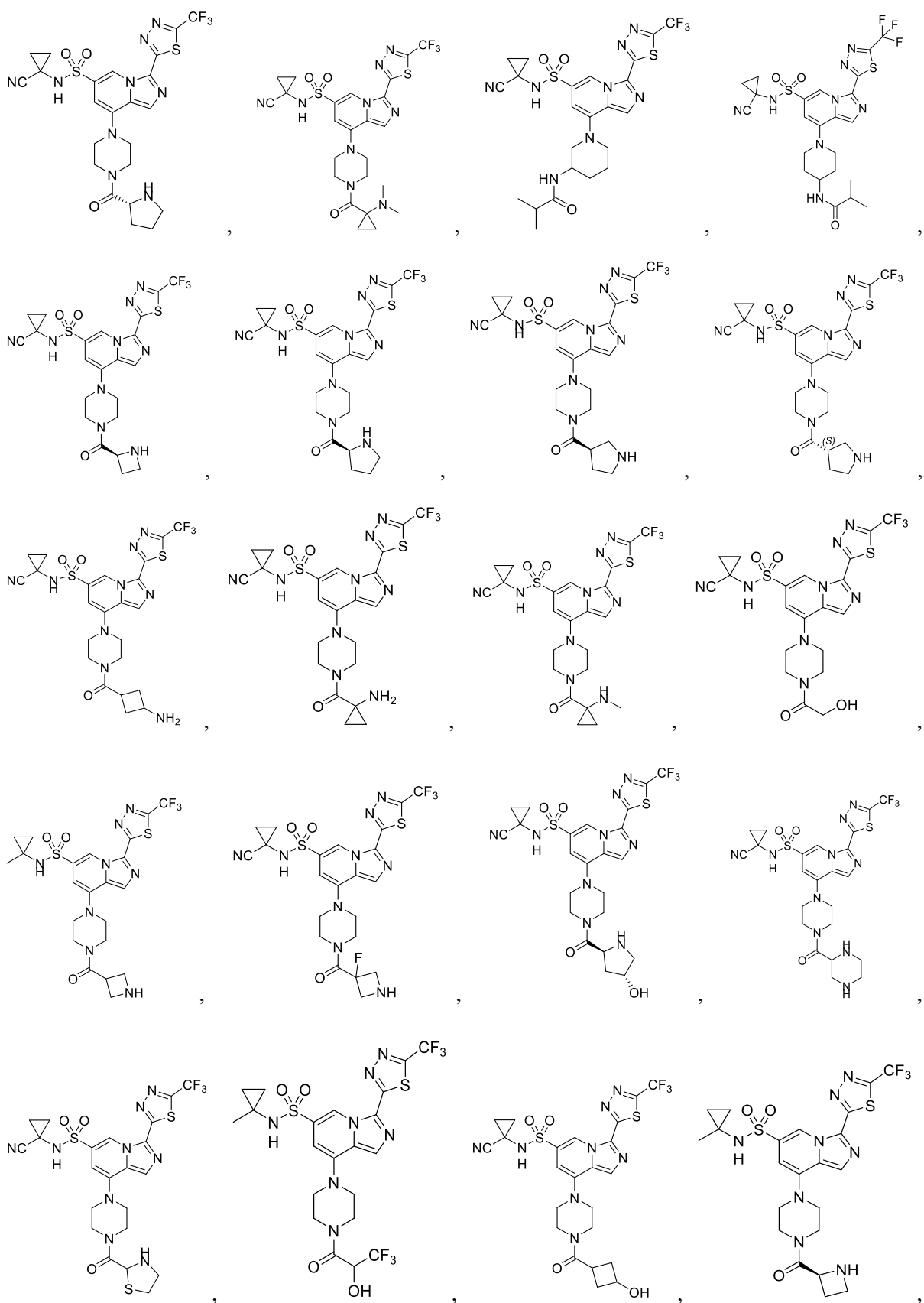


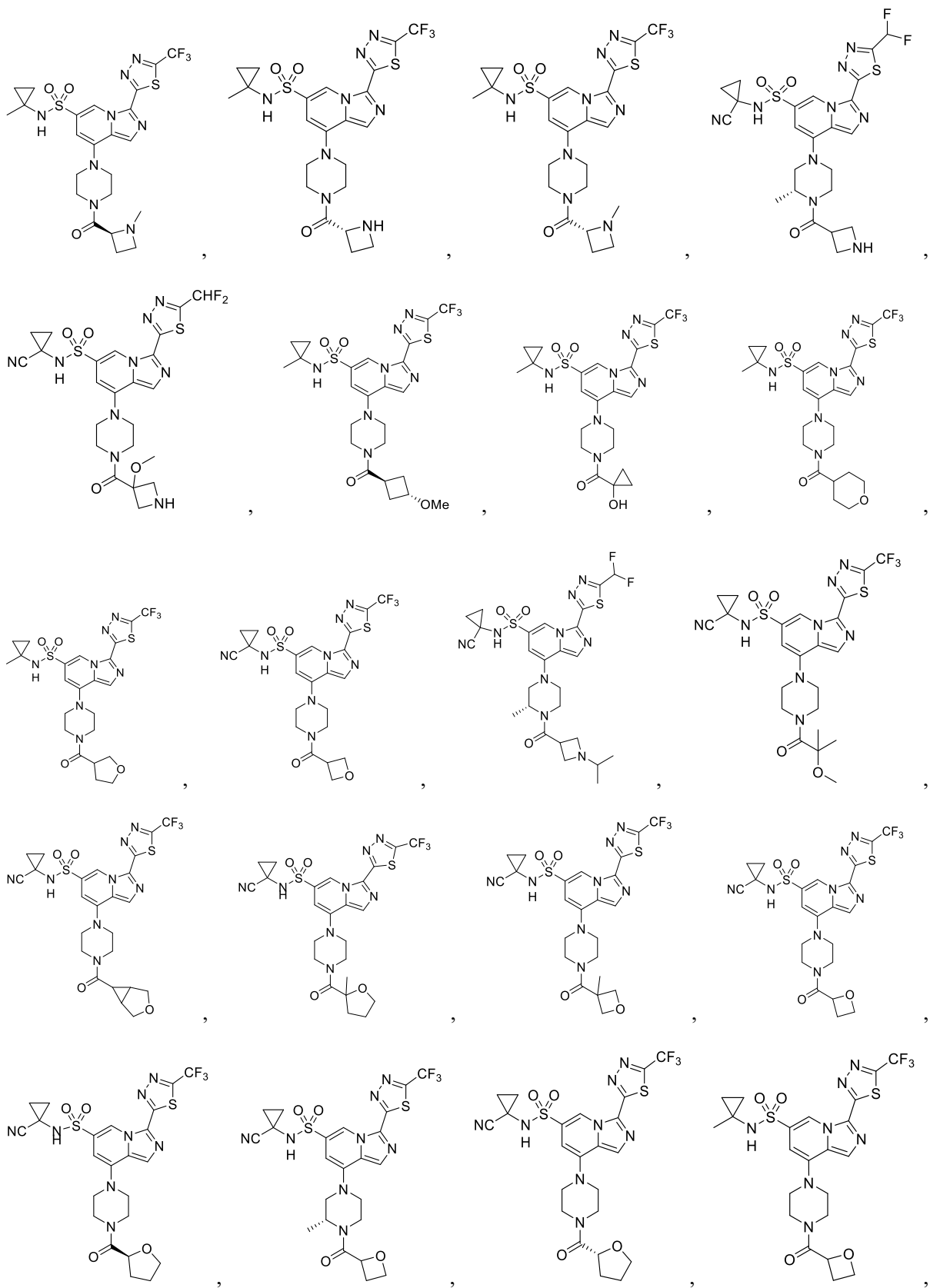


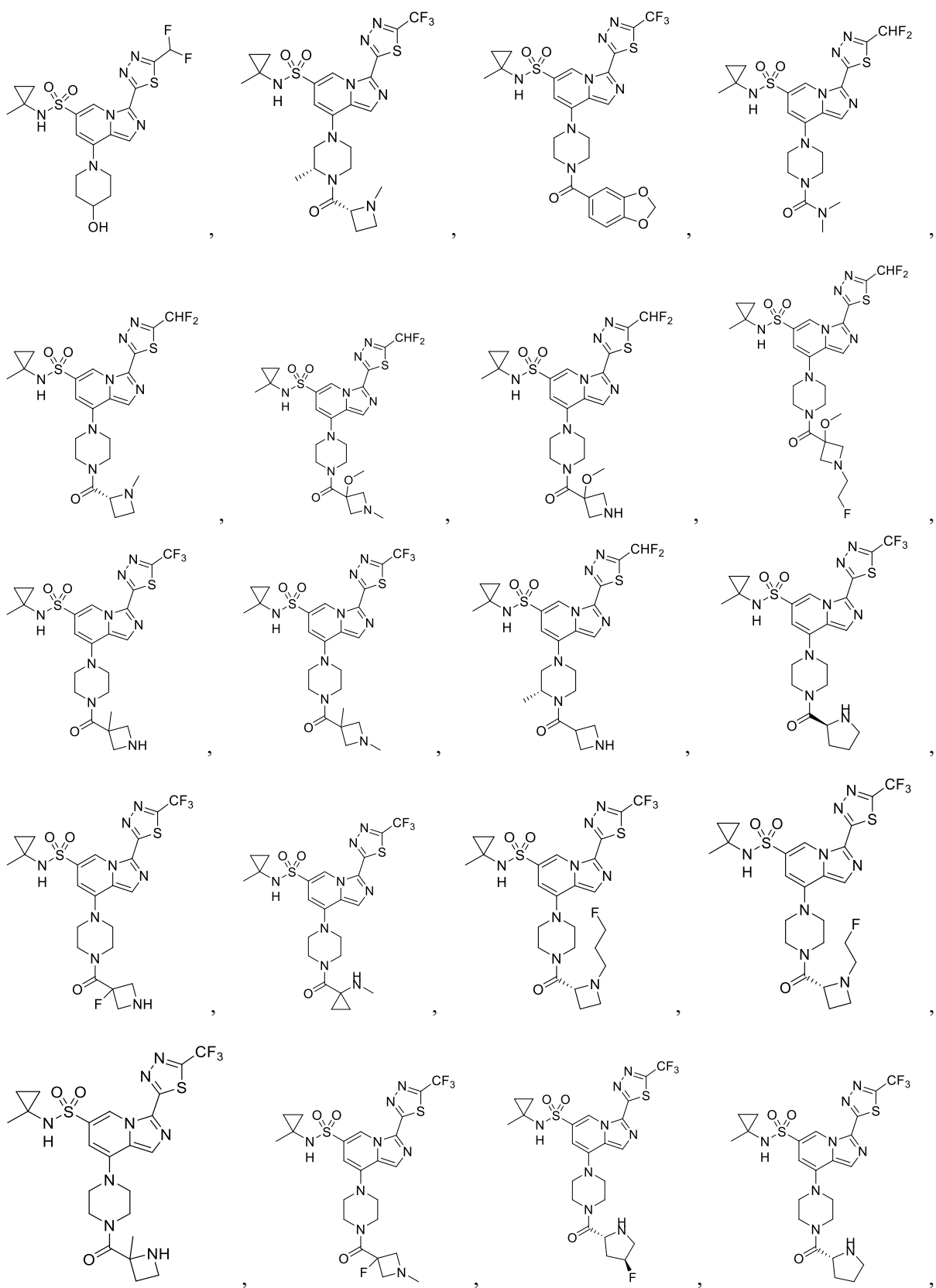


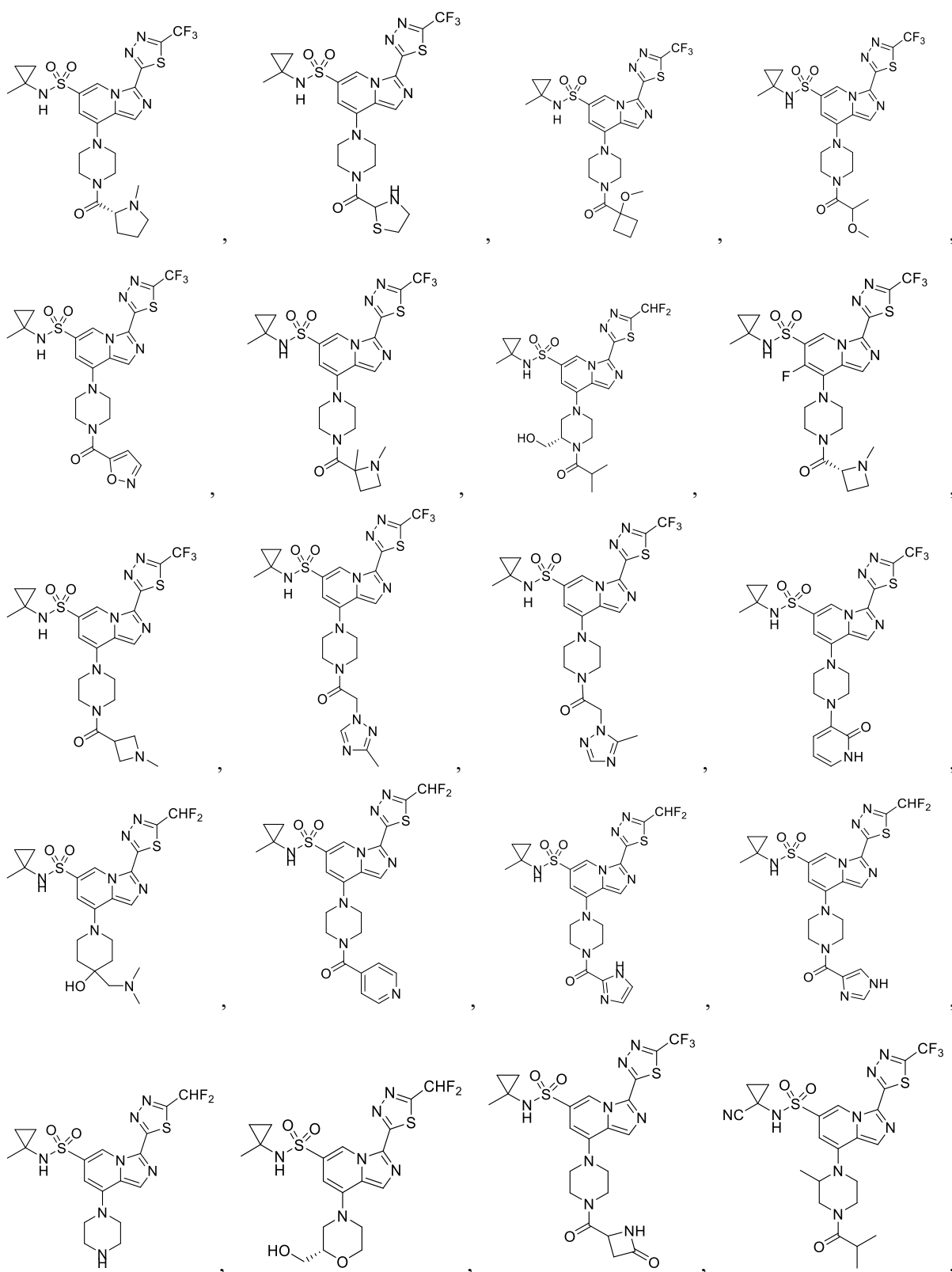


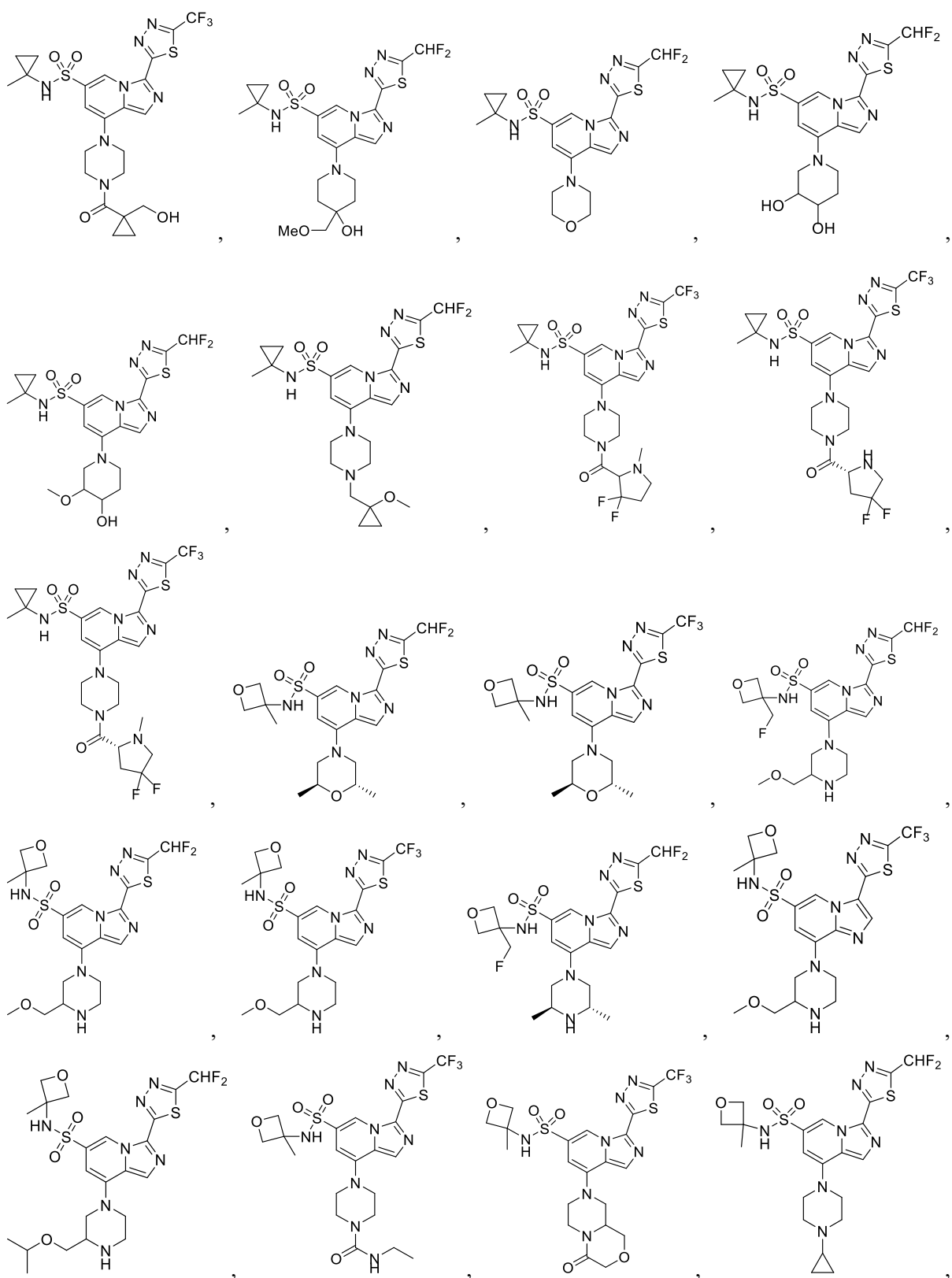


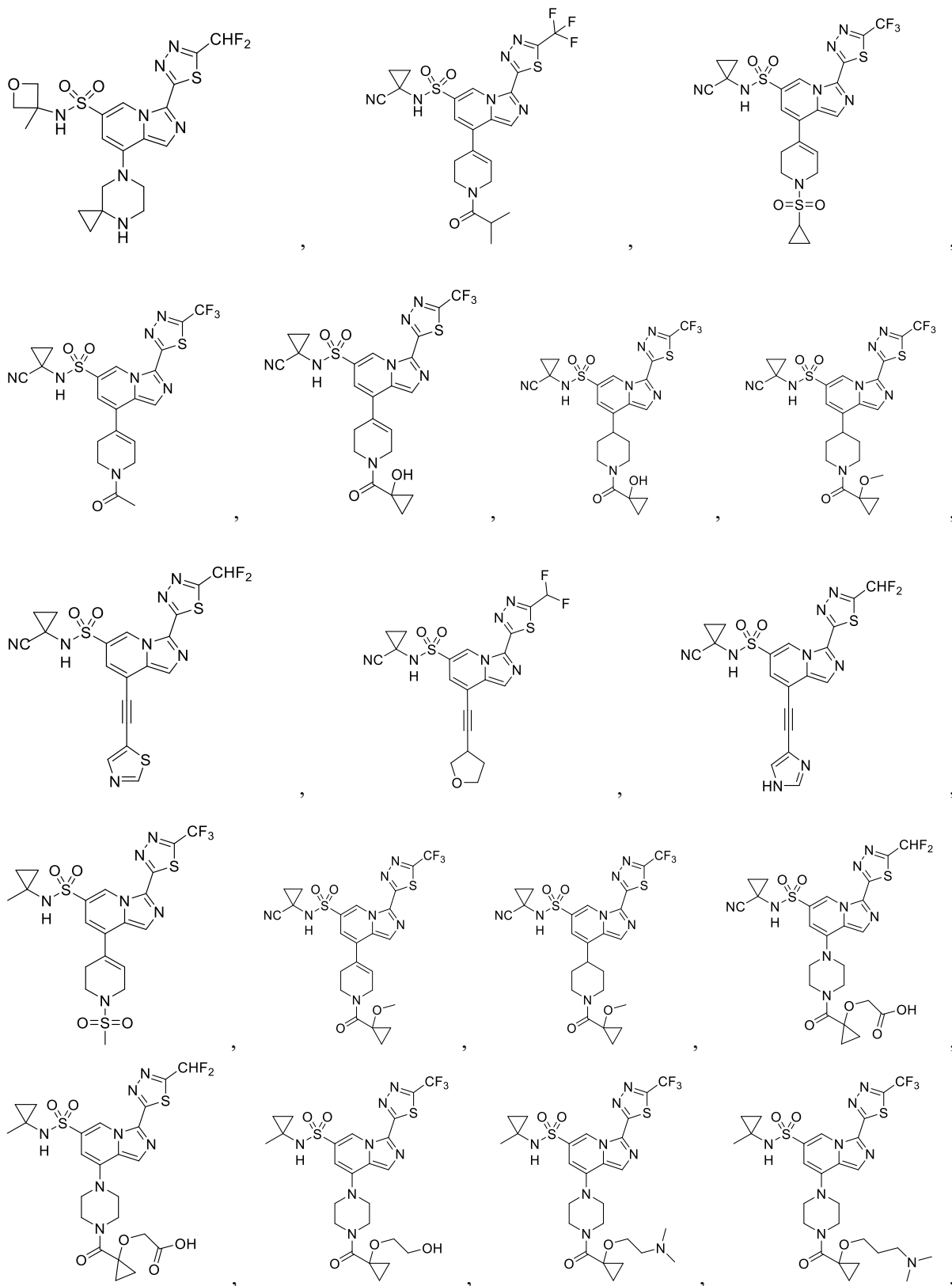


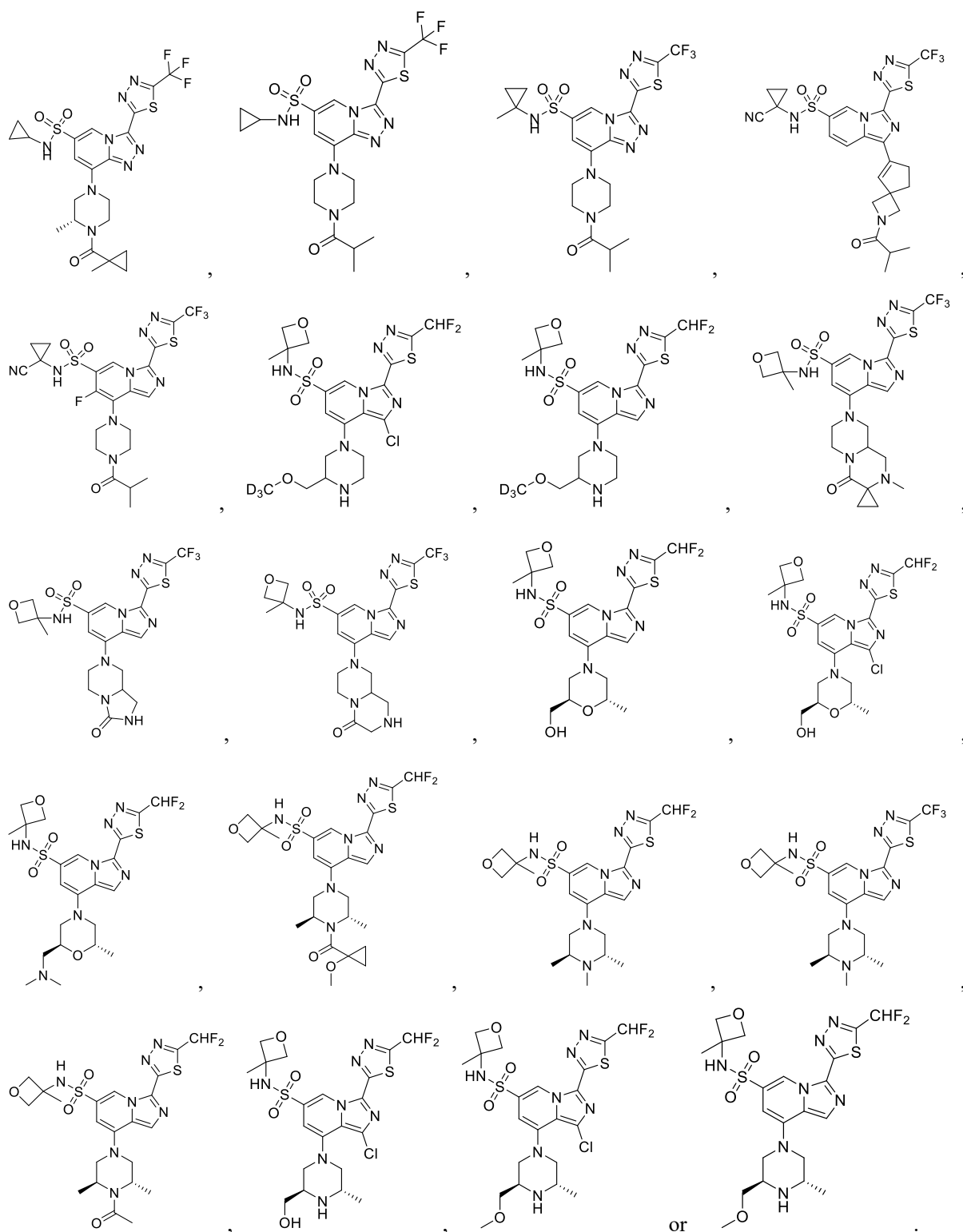






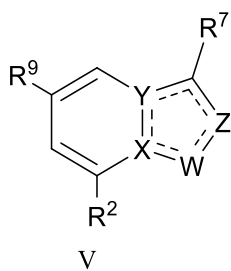
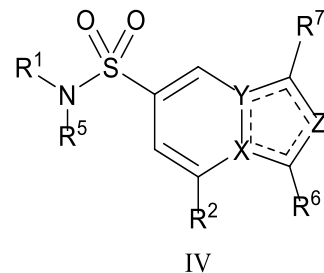
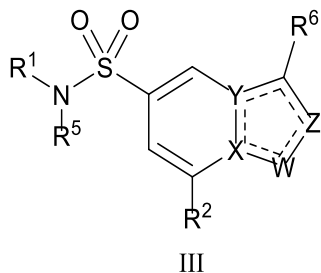
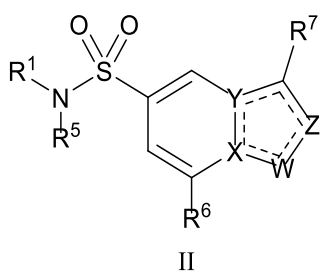






The present invention further provides a pharmaceutical composition, comprising a substance Z and a pharmaceutical excipient, wherein the substance Z is a compound of formula I, a pharmaceutically acceptable salt thereof or an isotopic compound thereof.

The present invention further provides use of a substance Z in preparation of a PARG inhibitor and a medicament for treating and/or preventing PARG-related diseases, wherein the substance Z is a compound of



wherein, R⁵ is hydrogen or PMB; R⁶ is halogen; R⁷ is R³, hydrogen or , R⁸ is hydrogen or

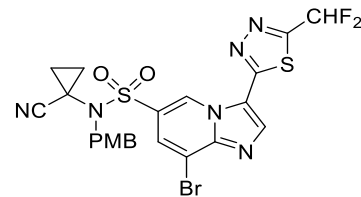
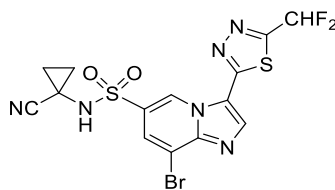
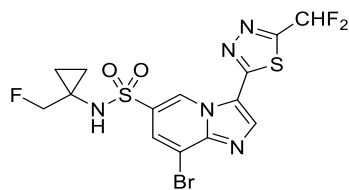
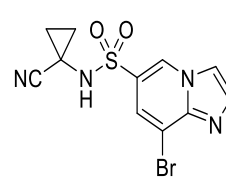
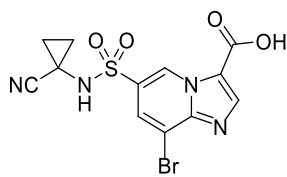
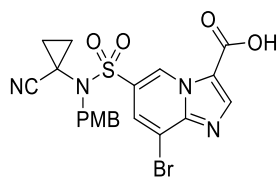
C₁-C₆ alkyl; R⁹ is , or halogen; and R¹, R², R³, X, Y, Z and W are as previously defined.

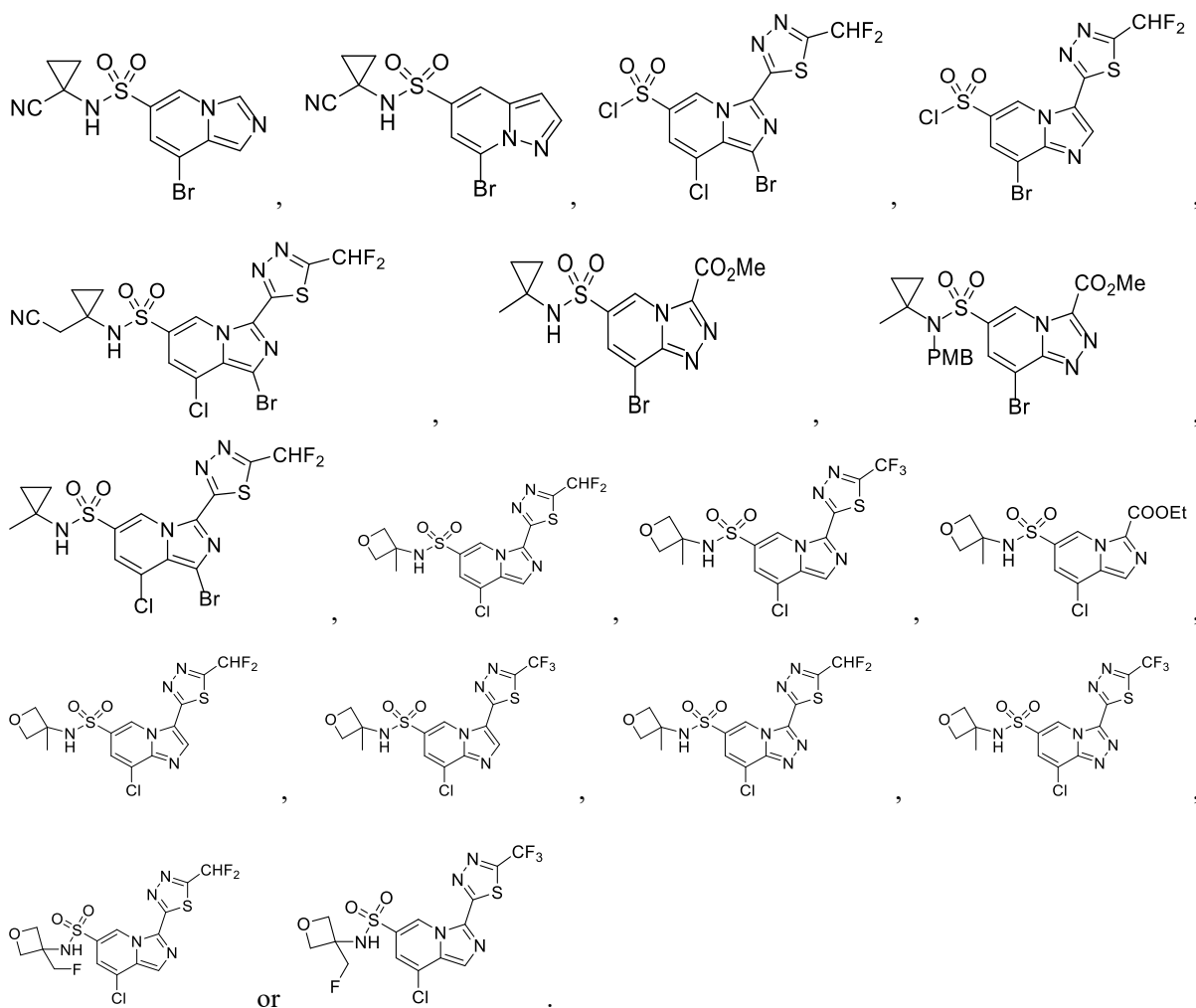
In a preferred embodiment, in R⁶, the halogen can be fluorine, chlorine, bromine or iodine, for example, chlorine or bromine.

In a preferred embodiment, in R⁸, the C₁-C₆ alkyl can be C₁-C₄ alkyl, and can also be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or ethyl.

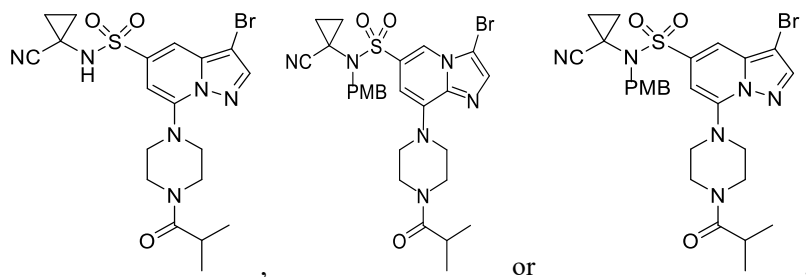
In a preferred embodiment, in R⁹, the halogen can be fluorine, chlorine, bromine or iodine, for example, chlorine or bromine.

In a preferred embodiment, the compound of formula II is of any one of the following structures:

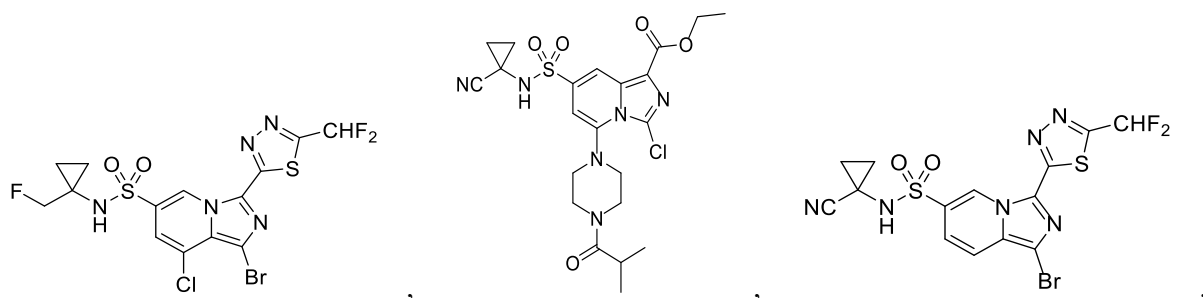


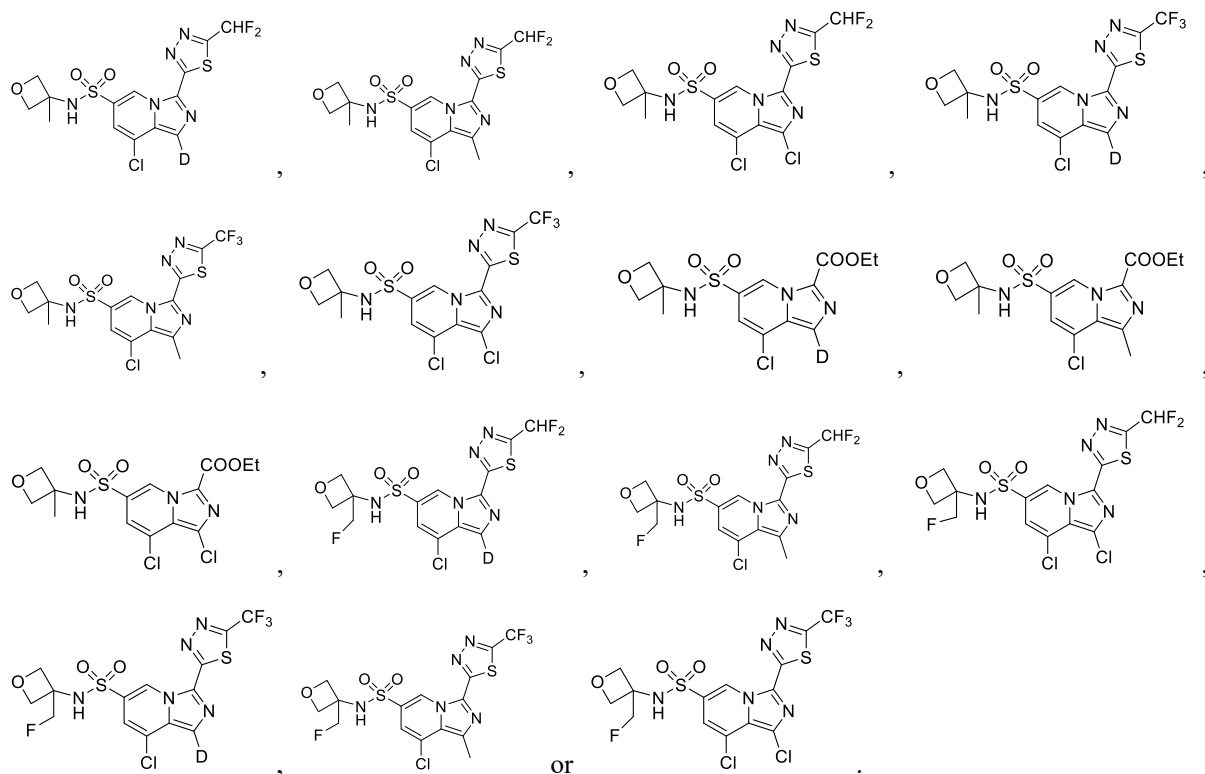


In a preferred embodiment, the compound of formula III is of any one of the following structures:

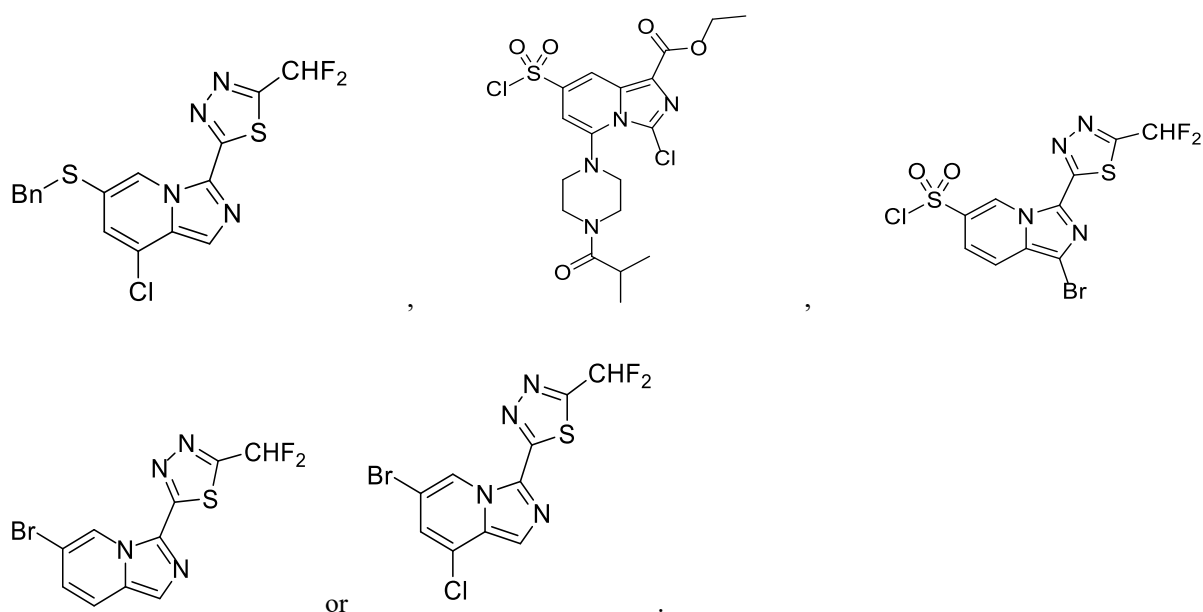


In a preferred embodiment, the compound of formula IV is of any one of the following structures:





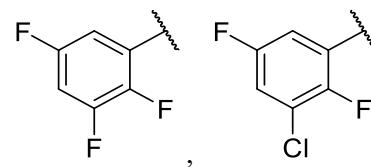
In a preferred embodiment, the compound of formula V is of any one of the following structures:



Interpretation of Terms

The term “a group B unsubstituted or substituted by more than one group A” means that one or more hydrogen atoms in the group B are independently substituted by the group A, or B is not substituted. When a plurality of groups A appear at the same time, their definitions are independent of each other without mutual influence, unless otherwise specified. For example, “C₆-C₁₀ aryl substituted by 3 halogens” means that

C₆-C₁₀ aryl is to be substituted by 3 halogens, the definitions of the 3 halogens are independent of each other



without mutual influence, and the halogens include but are not limited to:

or the like.

$\parallel$ has a double bond or a single bond.

The term “a plurality of” means 2 or more, for example 2, 3, 4, or 5.

The term “pharmaceutically acceptable” means a relatively non-toxic and safe condition suitable for use in patients.

The term “pharmaceutically acceptable salt” means the salt obtained by reacting a compound with a pharmaceutically acceptable acid or alkali. When the compound contains relatively acidic functional groups, an alkali addition salt may be obtained by contacting the compound with a sufficient amount of a pharmaceutically acceptable alkali in a suitable inert solvent. The pharmaceutically acceptable alkali addition salt includes, but is not limited to: a sodium salt, a potassium salt, a calcium salt, an aluminum salt, a magnesium salt, a bismuth salt, an ammonium salt or the like. When the compound contains relatively alkaline functional groups, an acid addition salt may be obtained by contacting the compound with a sufficient amount of a pharmaceutically acceptable acid in a suitable inert solvent. The pharmacologically acceptable acid addition salt includes, but is not limited to: hydrochloride, sulfate, formate, mesylate or the like. For details, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use (P. Heinrich Stahl, Camille G. Wermuth, 2011, 2nd Revised Edition).

“-” in the group means the fact that the group is attached to the rest of the molecule via this site. For example, CH₃-C(=O)- means acetyl.

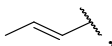
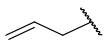
The term “halogen” means fluorine, chlorine, bromine or iodine. Halogen substitution in the present invention includes, but is not limited to, substitution by one, two, or three halogens, and in general, multiple substitutions occur on one carbon atom.

The term “oxo” means =O, indicating the substitution of two hydrogen on the same carbon atom by an oxygen atom. That is, a methylene group is substituted by a carbonyl group.

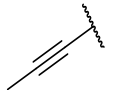
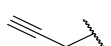
The term “alkyl” means a linear or branched saturated monovalent hydrocarbon group with a specified number of carbon atoms (for example, C₁-C₆). Alkyl groups include, but are not limited to: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-amyl, n-hexyl or the like.

The term “alkoxy” means the group R^X-O-, and R^X is defined in the same way as the term “alkyl”. Alkoxy groups include, but are not limited to: methoxy, ethoxy, n-propoxy, isopropoxy or the like.

The term “alkenyl” means a linear or branched unsaturated monovalent hydrocarbon group with a specified

number of carbon atoms (for example, C₂-C₆), with one or more (for example, 1, 2, or 3) carbon-carbon sp² double bonds. Alkenyl groups include, but are not limited to: vinyl, ,  or the like.

The term “alkynyl” means a linear or branched unsaturated monovalent hydrocarbon group with a specified number of carbon atoms (for example, C₂-C₆), with one or more (for example, 1, 2, or 3) carbon-carbon sp³

triple bonds. Alkynyl groups include, but are not limited to: acetylenyl, ,  or the like.

Unless otherwise specially stated in the present invention, the term “cycloalkyl” means a cyclic saturated monovalent hydrocarbon group with a specified number of carbon atoms (for example, C₃-C₁₀), which is monocyclic or polycyclic (for example, 2 or 3 rings, or a bridged, spiro or fused ring), and in the latter case, more than two carbon atoms are shared between the monocyclic rings. The monocyclic rings include, but are

not limited to: , , ,  or the like. The bridged-ring cycloalkenyl groups

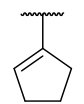
include, but are not limited to: , ,  or the like. The spiro-ring cycloalkenyl

groups include, but are not limited to, , ,  or the like. The

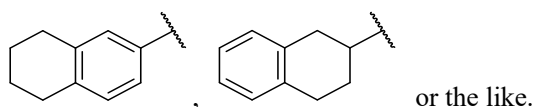
fused-ring cycloalkyl groups include, but are not limited to: , , ,

, , ,  or the like.

Unless otherwise specially stated in the present invention, the term “cycloalkenyl” refers to “cycloalkyl” having one or more carbon-carbon double bonds, and the “cycloalkyl” is defined as above. For example,



Unless otherwise specially stated in the present invention, the term “aryl” means a cyclic unsaturated monovalent hydrocarbon group with a specified number of carbon atoms (for example, C₆-C₁₀), which is monocyclic or polycyclic (for example, 2 or 3 rings). In case of a polycyclic ring, monocyclic rings share two atoms and a bond, and is (one or more/each ring is) aromatic. The aryl group is attached to the rest of a molecule by a ring that is aromatic or not. Aryl groups include, but are not limited to: phenyl, naphthyl,



Unless otherwise specially stated in the present invention, the term “heterocycloalkyl” means a monocyclic, bridged, spiro, or fused ring with a specified number of cyclic atoms (for example, 3-10 membered), a specified number of heteroatoms (for example, 1, 2 or 3), and a specified heteroatomic species (one or more selected from N, O and S). The in the latter case group can be saturated or unsaturated. A (monocyclic) heterocycloalkyl group is attached to the rest of a molecule by a carbon atom or heteroatom. The

monocyclic-ring heterocycloalkyl groups include, but are not limited to: ,

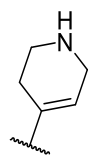
, or the like. The spiro-ring heterocycloalkyl groups include, but are not limited to:

, or the like. The bridged-ring heterocycloalkyl groups include,

but are not limited to: or the like. The fused-ring heterocycloalkyl groups include ,

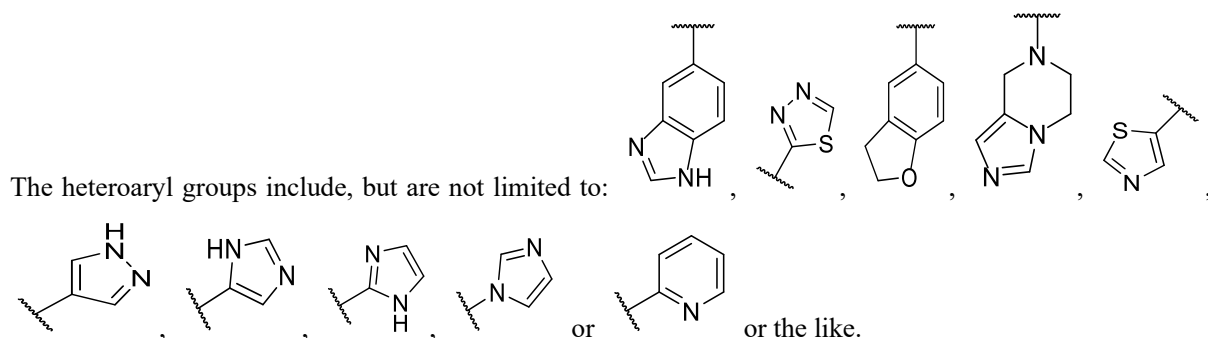
, or . Heterocycloalkyl unsaturation means the presence of a carbon-carbon

double bond or triple bond in the ring of the heterocycloalkyl, for example, , or



Unless otherwise specially stated in the present invention, the term “heteroaryl” means a cyclic unsaturated

monovalent group with a specified number of cyclic atoms (for example, 5-10 membered), a specified number of heteroatoms (for example, 1, 2 or 3), and a specified heteroatom species (one or more selected from N, O and S). It is monocyclic or polycyclic; and in the latter case, the monocyclic rings share two atoms and a bond, and at least one ring is aromatic. The heteroaryl group is attached to the rest of a molecule by a carbon atom or heteroatom, by a ring with or without heteroatoms, or by a ring that is aromatic or not.



The term “isotopic compound” means a compound in which one or more atom(s) have the isotopic abundance that differ from their natural abundance. For example, one or more atom(s) in a compound are substituted by an atom with a lower mass in nature, for instance, one hydrogen atom in a compound is substituted by deuterium, or C is substituted by ^{13}C .

Without departing from the common knowledge in the art, all the preferred conditions above can be randomly combined to implement the preferred embodiments of the present invention.

The reagents and raw materials used in the present invention are commercially available.

The positive effect of the present invention lies in that the compound of the present invention has a better PARC inhibitory activity. In addition, the compound of the present invention is greatly improved in permeability and/or solubility compared with the existing inventions.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be further illustrated below by the way of embodiments, which are not intended to limit the present invention. For the test methods without specific conditions indicated in the following embodiments, the specific conditions were selected according to conventional methods and conditions, or according to the product instructions.

All the compounds of the present invention may be synthesized with different methods by a person skilled in the field of organic chemistry. The following describes general synthesis schemes for preparing the compounds of the present invention. These schemes are generic, which, however, does not imply the limitation to the possible techniques used by a person skilled in the art to prepare the compounds disclosed herein. The different methods for preparing the compounds of the present invention are obvious to a person skilled in the art. In addition, the various steps in synthesis may be performed alternately in sequence to obtain one or more of the desired compounds. Examples of the preparation of the compounds of the present

invention by the method described in the general schemes are given in the Preparation and Examples sections described below. The preparation of compounds containing chiral center embodiments may be carried out by means of the techniques mastered by a person skilled in the art. For example, chiral compounds may be prepared by separating racemic products by chiral resolution by means of HPLC; or, example compounds may be prepared by known methods to obtain chiral compounds.

The chemical reactions and synthesis techniques described herein are performed in the reagents and solvents described herein, and the corresponding reaction yields are also affected by the reagents and solvents used. In addition, it should be understood that in the synthesis method described below, all the reaction conditions mentioned, including the choice of solvent, the reaction atmosphere, the reaction temperature, the experimental duration, and the feeding sequence for reaction, should be regarded as the standard operating conditions for the reaction, which should be easily identifiable by a person skilled in the art. Meanwhile, it is also understandable by a technician in the field of organic synthesis. The functional groups present on each part of a molecule must be compatible with the reagents used and the reaction itself. In case of the limitation of the incompatibility of some functional groups on each part of the molecule with the reaction conditions, an alternative method must be used, which is obvious to a person skilled in the art. To derive the desired compounds of the present invention, obviously, it is necessary to make judgement on the adjustment of the sequence of synthesis steps, or on the selection of a specific synthesis process scheme. This is understandable and easily recognizable to a person skilled in the field of organic synthesis. It should also be appreciated that another major consideration for any synthetic route designed in the art is the rational selection of a protective group to protect the tolerance of reactive functional groups present in the compounds described in the present invention. For details, a reference can be made to the work of Greene et al., authorities in the field of chemistry (*Protective Groups in Organic Synthesis*, Third Edition, Wiley and Sons (1999)).

Examples

The compounds and the intermediates used in the preparation of the compounds may be prepared using the procedures shown in the following examples and related procedures. The methods and conditions used in these examples and the actual compounds prepared in these examples are not meant to be limited, but imply to elaborate how to prepare the relevant compounds. The starting materials and reagents used in these examples, when not prepared by the procedures described herein, are often commercially available, or have been reported in the relevant chemical literature, or may be prepared by using the procedures described in the chemical literature.

In the examples given herein, the term “drying and concentrating” generally means the addition of an anhydrous sodium sulfate or magnesium sulfate drying solution to an organic solvent, followed by filtration and removal of the solvent from the filtrate (usually under reduced pressure and at a temperature suitable for the stability of the compound being prepared). In case of chromatographic column methods, conventional

column chromatography or rapid column chromatography is typically used for column separation and purification, or a medium-pressure chromatograph (Biotage Isola One) preloaded with silica-gel column is used for elution in a specified solvent or solvent mixture. In some cases, the final product is rapidly purified by preparative thin-layer chromatography using silica gel plates of 20 cm x 20 cm x 0.5 mm or 20 cm x 20 cm x 1 mm in an appropriate solvent system. Preparative high-performance liquid chromatography (HPLC) is performed using a reversed-phase column (Waters Sunfire C18, Waters Xbridge C18, or a similar reversed-phase column) with a size appropriate for the amount of compound being separated; elution is typically performed by adding methanol or acetonitrile of gradient concentrations to an aqueous phase, with an eluent containing 0.05% or 0.1% formic acid, trifluoroacetic acid, or 10 mM ammonium acetate, at an elution rate matching the size of the reversed-phase column used and the resolution of the product to be prepared. The chemical names used herein are generated using ChemDraw Professional version 19.1 and then translated into Chinese.

List of Abbreviations

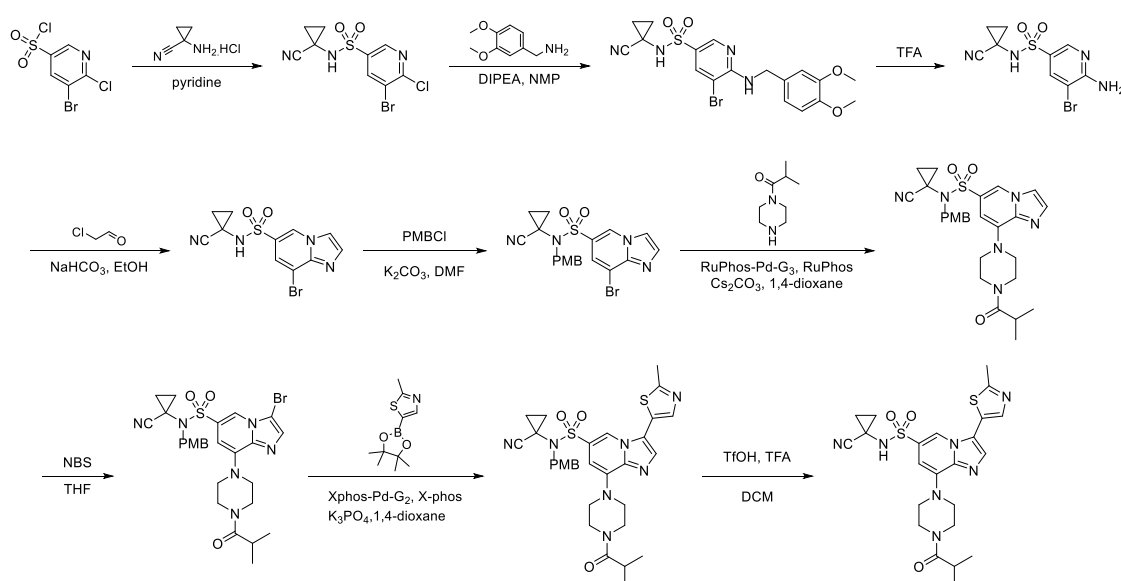
Abbreviation	Full name	Abbreviation	Full name
MS	Mass spectrometry	NMR	Nuclear magnetic resonance
TLC	Thin-layer chromatography	HPLC	High performance liquid chromatography
LCMS	Liquid chromatography-mass spectrometry	DMF	N,N-dimethylformamide
DCE	1,2-dichloroethane	PE	Petroleum ether
DCM	Dichloromethane	DMSO	Dimethyl sulfoxide
MTBE	Methyl tert-butyl ether	THF	Tetrahydrofuran
EA	Ethyl acetate	T3P	1-propylphosphoric anhydride
Pd(dppf)Cl ₂	[1,1'-di(diphenylphosphino)-ferrocen]palladium dichlorid(II)	HATU	2-(7-azobenzotriazol)-N,N,N',N'-tetramethyluronium hexafluorophosphate
TFA	Trifluoroacetic acid	TEA	Triethylamine
NCS	N-chlorosuccinimide	NBS	N-bromosuccinimide
NBS	N-bromosuccinimide	DAST	Diethylaminosulphur trifluoride
XantPhos	4,5-bisdiphenylphosphino-9,	Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)

	9-dimethylxanthene		dipalladium
MsCl	Methylsulfonyl chloride	RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl
RuPhos Pd G3	Methanesulfonato(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)(2-amino-1,1'-biphenyl-2-yl)palladium (II)	XPhos Pd G2	Chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2-amino-1,1'-biphenyl)]palladium (II)
NMP	N-methyl pyrrolidone	Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl		

Example

1:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step 1: 5-bromo-6-chloro-N-(1-cyanocyclopropyl)pyridine-3-sulfonamide

At 0°C, 5-bromo-6-chloropyridin-3-sulfonyl chloride (3.3 g, 27.5 mmol) was added portionwise into the solution of 1-aminocyclopropan-1-yl cyano hydrochloride (4 g, 13.7 mmol) in pyridine (20 mL); and then, the resulting mixture was stirred for 1 hour at room temperature. The mixture was acidified to pH~5 using 1N hydrochloric acid, and extracted with ethyl acetate twice. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound

(yellow solid, 4 g, yield: 86.4%). LC/MS (ESI) m/z : 336 $[M+H]^+$.

Step 2: 5-bromo-N-(1-cyanocyclopropyl)-6-((3,4-dimethoxybenzyl)amino)pyridin-3-sulfonamide

N,N-diisopropylethylamine (4.6 g, 35.6 mmol) and (3,4-dimethoxyphenyl)methylamine (3.0 g, 17.8 mmol) were dropwise added slowly to the solution of 5-bromo-6-chloro-N-(1-cyanocyclopropyl)pyridin-3-sulfonamide (4 g, 11.9 mmol) in N-methyl pyrrolidone (40 mL). The mixture was stirred at 100°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature; water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 5.1 g, yield: 91.7%). LC/MS (ESI) m/z : 469 $[M+H]^+$.

Step 3: 6-amino-5-bromo-N-(1-cyanocyclopropyl)pyridine-3-sulfonamide

At 0°C, 5-bromo-N-(1-cyanocyclopropyl)-6-((3,4-dimethoxybenzyl)amino)pyridin-3-sulfonamide (5.0 g, 10.7 mmol) was dissolved in trifluoroacetic acid (20 mL). The reaction mixture was stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure to obtain the title compound (yellow solid, 3.39 g, yield: 100.0%), which was directly used in the next step without purification. LC/MS (ESI) m/z : 319 $[M+H]^+$.

Step 4: 8-bromo-N-(1-cyanocyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

Sodium bicarbonate (2.7 g, 32.1 mmol) and 2-chloroacetaldehyde (8.5 mL, 53.5 mmol, 40% aqueous solution) were slowly added into the solution of 6-amino-5-bromo-N-(1-cyanocyclopropyl)pyridin-3-sulfonamide (3.39 g, 10.7 mmol) in ethanol (100 mL), and the reaction mixture was stirred at 90°C overnight. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to dryness. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 1.5 g, yield: 41.1%). ^1H NMR (400 MHz, DMSO- d_6) δ 9.37 (d, J = 1.6 Hz, 1H), 8.31 (d, J = 1.2 Hz, 1H), 7.80 (d, J = 1.2 Hz, 1H), 7.74 (d, J = 1.6 Hz, 1H), 1.49 - 1.45 (m, 2H), 1.38 - 1.33 (m, 2H). LC/MS (ESI) m/z : 343 $[M+H]^+$.

Step 5: 8-bromo-N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

Potassium carbonate (790 mg, 5.7 mmol) and 1-(chloromethyl)-4-methoxybenzene (454 mg, 2.9 mmol) were added into the solution of 8-bromo-N-(1-cyanocyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (650 mg, 1.9 mmol) in N,N-dimethylformamide (5 mL). The reaction mixture was stirred at 45°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature; water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl

acetate) to obtain the title compound (yellow solid, 720 mg, yield: 81.9%). LC/MS (ESI) m/z: 461 [M+H]⁺.

Step

6:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

Cesium carbonate (805 mg, 2.47 mmol), RuPhos (115 mg, 0.25 mmol) and RuPhos Pd G3 (103 mg, 0.12 mmol) were added into the solution of 8-bromo-N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (570 mg, 1.24 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (386 mg, 2.47 mmol) in 1,4-dioxane (12 mL). The reaction mixture was stirred at 110°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature; water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-4% methanol) to obtain the title compound (yellow solid, 530 mg, yield: 79.9%). LC/MS (ESI) m/z: 537 [M+H]⁺.

Step

7:

3-bromo-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At -10°C, the solution of N-bromosuccinimide (176 mg, 0.99 mmol) in tetrahydrofuran (7.5 mL) was slowly added into the solution of N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (530 mg, 0.99 mmol) in tetrahydrofuran (15 mL). The mixture was stirred at room temperature for 30 minutes. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (eluent: dichloromethane/methanol, gradient: 0-4% methanol) to obtain the title compound (yellow solid, 430 mg, yield: 70.7%). LC/MS (ESI) m/z: 617 [M+H]⁺.

Step

8:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Potassium phosphate (52 mg, 0.24 mmol), XPhos (4 mg, 0.008 mmol) and XPhos Pd G2 (6 mg, 0.008 mmol) were sequentially added into the mixed solution of 3-bromo-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (50 mg, 0.08 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (37 mg, 0.16 mmol) in 1,4-dioxane (3 mL) and water (0.6 mL). The reaction mixture was stirred at 100°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature; water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

The residue was purified by column chromatography (eluent: dichloromethane/methanol, gradient: 0-5% methanol) to obtain the title compound (yellow solid, 17 mg, yield: 34.0%). LC/MS (ESI) m/z : 634 $[M+H]^+$.

Step

9:

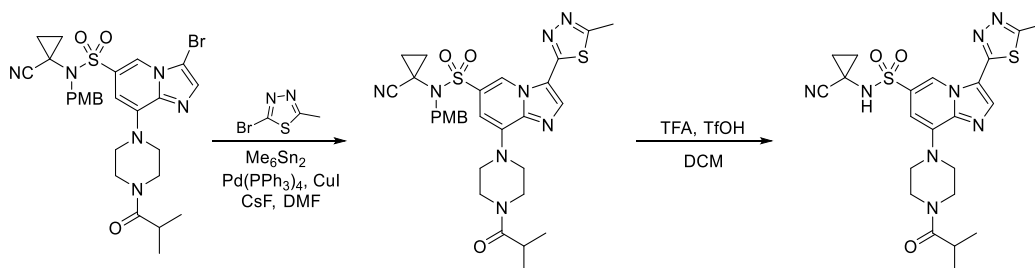
N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (0.1 mL) and trifluoromethanesulfonic acid (0.1 mL) were dropwise added slowly into the solution of N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-6-sulfonamide (17 mg, 0.03 mmol) in dichloromethane (0.5 mL). The mixture was stirred at room temperature for 30 minutes. The mixture was concentrated, and the residue was purified by pre-HPLC to obtain the title compound (white solid, 5 mg, yield: 36.3%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.38 (d, J = 1.2 Hz, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 6.77 (d, J = 1.1 Hz, 1H), 3.77 - 3.57 (m, 8H), 2.95 (dt, J = 13.5, 6.7 Hz, 1H), 2.78 (s, 3H), 1.46 (dd, J = 8.3, 5.4 Hz, 2H), 1.33 (dd, J = 8.4, 5.5 Hz, 2H), 1.04 (d, J = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 514 $[M+H]^+$.

Example

2:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step

1:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

At room temperature, hexamethylditin (0.067 mL, 0.324 mmol), CsF (49 mg, 0.32 mmol) and CuI (6.2 mg, 0.032 mmol) were sequentially added into the solution of 3-bromo-N-(1-cyanocyclopropyl)-N-[(4-methoxyphenyl)methyl]-8-[4-(2-methylpropionyl)piperazin-1-yl]imidazo[1,2-a]pyridine-6-sulfonamide (100 mg, 0.16 mmol) and 2-bromo-5-methyl-1,3,4-thiadiazole (58 mg, 0.32 mmol) in DMF (3 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 100°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched by adding water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The

residue was purified by silica gel chromatography (eluent: dichloromethane/ methanol, gradient: 0-3% methanol) to obtain the title compound (yellow solid, 30 mg, yield: 29.1%). LC/MS (ESI) m/z : 635 $[M+H]^+$.

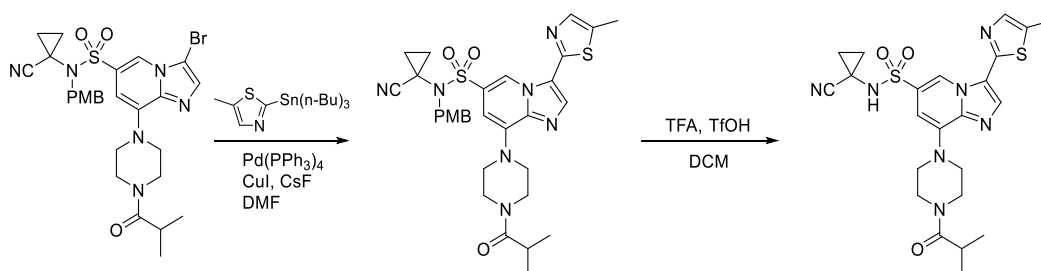
Step 2:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the preparation method in Step 9 of **Example 1**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.78 (s, 1H), 9.42 (s, 1H), 8.44 (s, 1H), 7.02 - 6.91 (m, 1H), 3.81 - 3.71 (m, 4H), 3.69 - 3.59 (m, 4H), 3.01 - 2.91 (m, 1H), 2.83 (s, 3H), 1.53 - 1.33 (m, 4H), 1.09 - 0.99 (m, 6H). LC/MS (ESI) (m/z): 515 $[M+H]^+$.

Example 3:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-methylthiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step 1:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(5-methylthiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

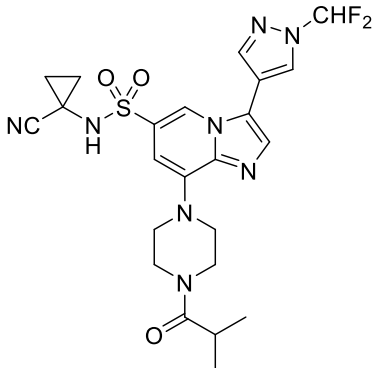
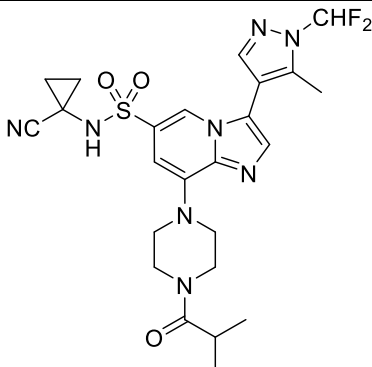
At room temperature, CuI (2 mg, 0.008 mmol), CsF (37 mg, 0.24 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (9 mg, 0.008 mmol) were sequentially added into the solution of 3-bromo-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (50 mg, 0.08 mmol) and 5-methyl-2-(tri-n-butylstannyl)thiazole (63 mg, 0.16 mmol) in DMF (2 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 100°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched by adding water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: dichloromethane/ methanol, gradient: 0-4% methanol) to obtain the title compound (yellow solid, 30 mg, yield: 58.2%). LC/MS (ESI) m/z : 634 $[M+H]^+$.

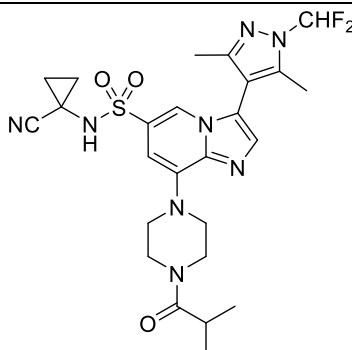
Step 2:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-methylthiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the synthesis method in Step 9 of **Example 1**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.80 (s, 1H), 8.29 (s, 1H), 7.76 (s, 1H), 6.88 (s, 1H), 3.80 - 3.56 (m, 8H), 3.01 - 2.91 (m, 1H), 2.54 (s, 3H), 1.49 - 1.42 (m, 2H), 1.40 - 1.33 (m, 2H), 1.04 (d, J = 6.3 Hz, 6H). LC/MS (ESI) (m/z): 514 $[\text{M}+\text{H}]^+$.

By referring to the preparation methods in Examples 1, 2 and 3, the following examples were implemented by synthesizing crude products according to a similar route by starting from appropriate starting materials, preparing the crude products via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

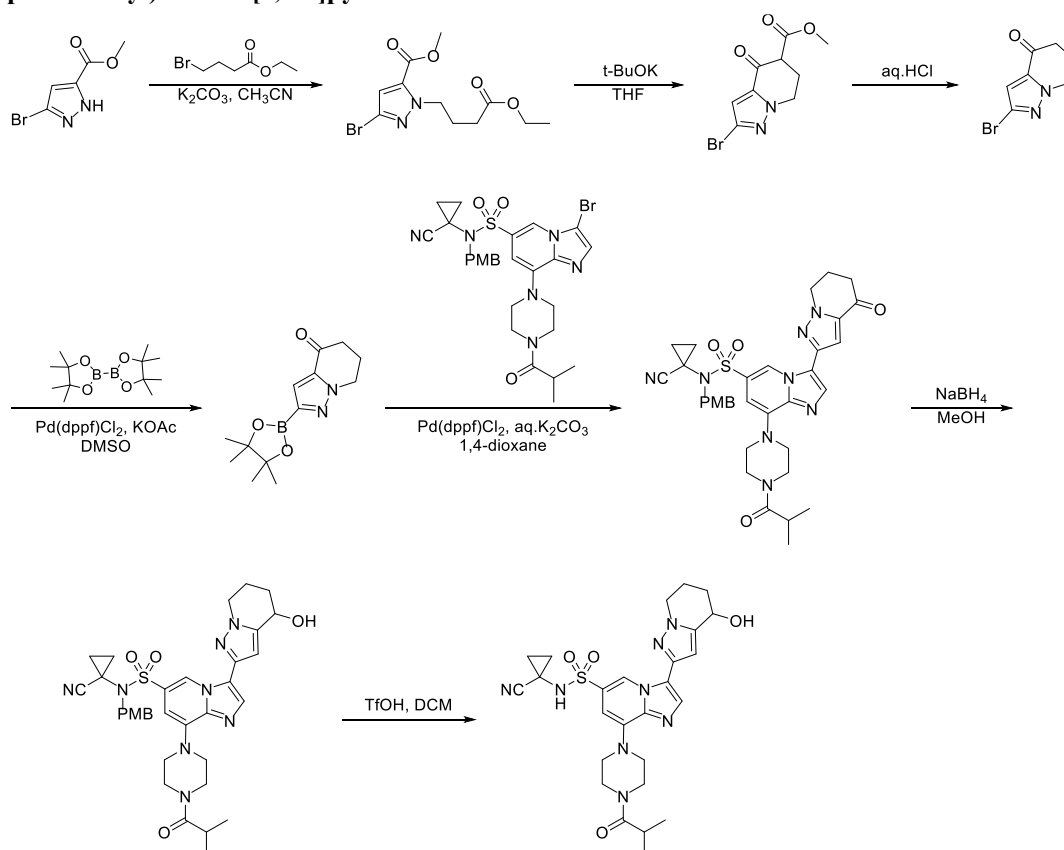
Example	Structure and name	Analysis data
Example 4	 N-(1-cyanocyclopropyl)-3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.28 (s, 1H), 8.81 (s, 1H), 8.32 (d, J = 1.4 Hz, 1H), 8.27 (s, 1H), 8.12 - 7.83 (m, 2H), 6.76 (d, J = 1.3 Hz, 1H), 3.76 - 3.59 (m, 8H), 2.99 - 2.92 (m, 1H), 1.50 - 1.43 (m, 2H), 1.37 - 1.31 (m, 2H), 1.05 (d, J = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 533 $[\text{M}+\text{H}]^+$.
Example 5	 N-(1-cyanocyclopropyl)-3-(1-(difluoromethyl)-5-methyl-1H-pyrazol-4-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.28 (s, 1H), 8.81 (s, 1H), 8.32 (d, J = 1.4 Hz, 1H), 8.12 - 7.83 (m, 2H), 6.76 (d, J = 1.3 Hz, 1H), 3.76 - 3.59 (m, 8H), 2.99 - 2.92 (m, 1H), 2.27 (s, 3H), 1.50 - 1.43 (m, 2H), 1.37 - 1.31 (m, 2H), 1.05 (d, J = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 547 $[\text{M}+\text{H}]^+$.

Example 6	 N-(1-cyanocyclopropyl)-3-(1-(difluoromethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.29 (s, 1H), 8.03 - 7.72 (m, 3H), 6.76 - 6.70 (m, 1H), 3.79 - 3.61 (m, 8H), 3.01 - 2.91 (m, 1H), 2.28 (s, 3H), 2.07 (s, 3H), 1.46 - 1.39 (m, 2H), 1.39 - 1.32 (m, 2H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 561 [M+H]⁺.
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Example

7:

N-(1-cyanocyclopropyl)-3-(4-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step 1: Methyl 3-bromo-1-(4-ethoxy-4-oxobutyl)-1H-pyrazole-5-carboxylate

At 0°C, potassium carbonate (2 g, 14.6 mmol) and 4-ethyl bromobutyrates (2.3 g, 12 mmol) were added into the solution of 3-bromo-1H-pyrazol-5-methyl carboxylate (2.0 g, 9.7 mmol) in acetonitrile (20 mL), and the

resulting mixture was stirred at 80°C for 8 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched by adding ice water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (white solid, 3.0 g, yield: 96.4%).

Step 2: Methyl 2-bromo-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylate

At 0°C, potassium tert-butoxide (1.6 g, 14 mmol) was added into the solution of 3-bromo-1-(4-ethoxy-4-oxybutyl)-1H-pyrazol-5-methyl carboxylate (3 g, 9.4 mmol) in tetrahydrofuran (30 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 50°C for 8 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, poured into ice water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (white solid, 1.4 g, yield: 54.5%).

Step 3: 2-bromo-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one

At room temperature, 2-bromo-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-5-methyl formate (1.4 g, 5.1 mmol) was added into concentrated hydrochloric acid (20 mL), and the reaction mixture was stirred at 90°C for 16 hours. After completion of the reaction, at 0°C, the reaction mixture was neutralized with 1N sodium hydroxide in water, and extracted with ethyl acetate twice. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (colorless oil, 0.53 g, yield: 48.1%). ¹H NMR (400 MHz, CDCl₃) δ 6.77 (s, 1H), 4.35 - 4.22 (m, 2H), 2.69 - 2.57 (m, 2H), 2.37 - 2.24 (m, 2H). LC/MS (ESI) m/z: 216 [M+H]⁺.

Step 4: 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one

Under the nitrogen atmosphere at room temperature, potassium acetate (760 mg, 7.5 mmol), XPhos (250 mg, 0.5 mmol) and Pd₂(dba)₃ (225 mg, 0.2 mmol) were added into the solution of 2-bromo-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one (530 mg, 2.5 mmol) and bis(pinacolato)diboron (1.25 g, 4.9 mmol) in 1,4-dioxane (10 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature; ice water was added into the reaction mixture; and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (colorless oil, 380 mg, yield: 48.0%). LC/MS (ESI) m/z: 263 [M+H]⁺.

Step

5:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, potassium carbonate (120 mg, 0.8 mmol) and Pd(dppf)Cl₂ (25 mg, 0.03 mmol) were added into the solution of 3-bromo-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (150 mg, 0.26 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one (120 mg, 0.5 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL). The flask was replaced with nitrogen gas three times and then the mixture was allowed to react for 3 hours at 90°C under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (yellow solid, 110 mg, yield: 28.7%). LC/MS(ESI) m/z: 671 [M+H]⁺.

Step

6:

N-(1-cyanocyclopropyl)-3-(4-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, sodium borohydride (10 mg, 0.3 mmol) was added into the solution of N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(4-carbonyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide (100 mg, 0.1 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction was subjected acid quenching using 1N dilute hydrochloric acid, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (yellow solid, 70 mg, yield: 80%). LC/MS (ESI) m/z: 673 [M+H]⁺.

Step

7:

N-(1-cyanocyclopropyl)-3-(4-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

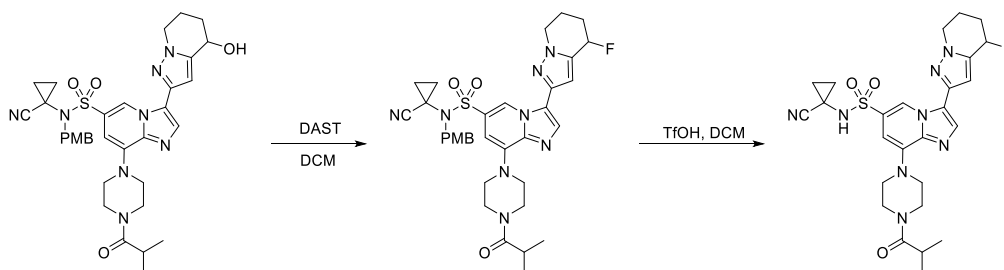
At 0°C, TfOH (0.1 mL) was added into the solution of N-(1-cyanocyclopropyl)-3-(4-hydroxy)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (30 mg, 0.04 mmol) in dichloromethane (0.5 mL), and the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the mixture was concentrated to dryness, and residue was purified by pre-HPLC to obtain the title compound (white solid, 6.3 mg, yield: 25.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.58 (s, 1H), 8.08 (s, 1H), 6.76 (s, 1H), 6.75 (s, 1H), 5.58 (d, *J* = 5.5 Hz, 1H), 4.84 - 4.75 (m, 1H), 4.20 - 4.14 (m,

2H), 3.77 - 3.69 (m, 4H), 3.68 - 3.56 (m, 4H), 3.00 - 2.91 (m, 1H), 2.27 - 2.15 (m, 1H), 2.10 - 1.93 (m, 2H), 1.82 - 1.69 (m, 1H), 1.47 - 1.30 (m, 4H), 1.05 (d, $J = 6.5$ Hz, 6H). LC/MS (ESI) (m/z): 553 $[M+H]^+$.

Example

8:

N-(1-cyanocyclopropyl)-3-(4-fluoro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step

1:

N-(1-cyanocyclopropyl)-3-(4-fluoro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, diethylaminosulphur trifluoride (18 mg, 0.11 mmol) was dropwise dropped to the solution of N-(1-cyanocyclopropyl)-3-(4-hydroxyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (40 mg, 0.06 mmol) in dichloromethane (0.5 mL); and the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was quenched using saturated sodium bicarbonate in water at 0°C, and extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow oil, 25 mg, yield: 74.9%), with the crude product directly used in the next reaction. LC/MS (ESI) (m/z): 675 $[M+H]^+$.

Step

2:

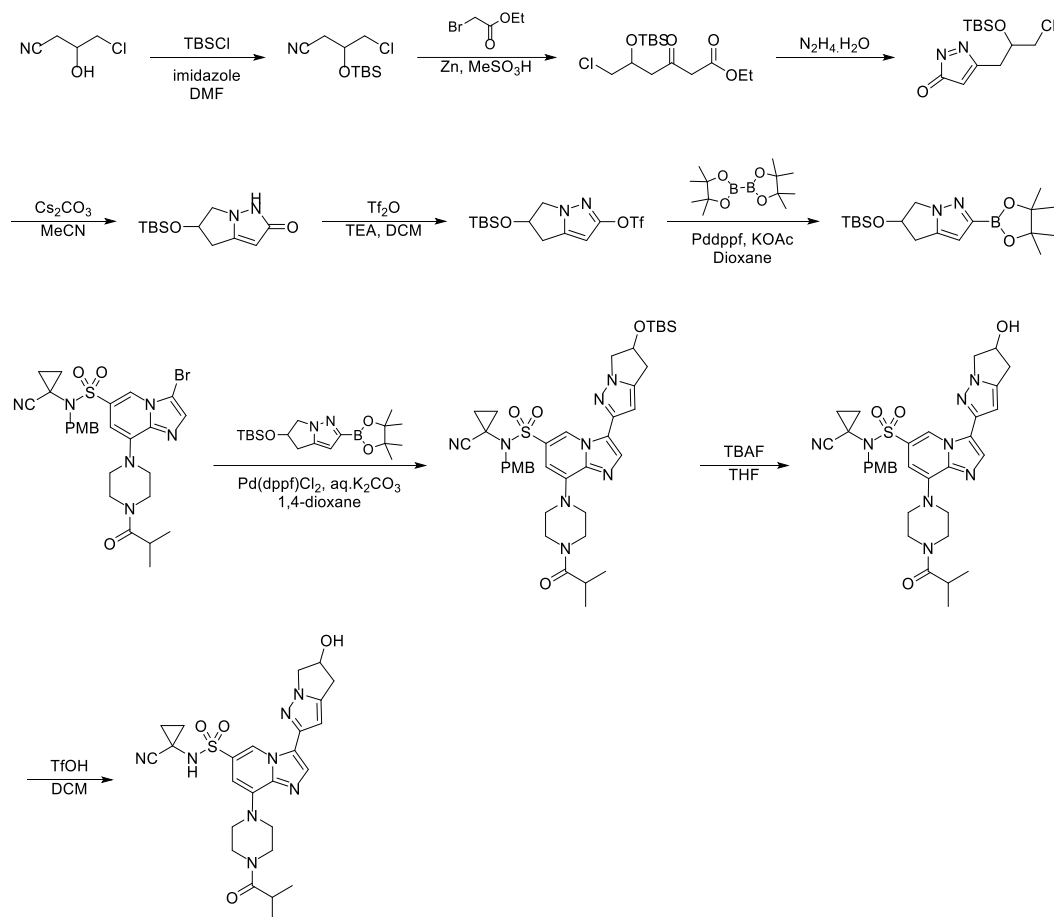
N-(1-cyanocyclopropyl)-3-(4-fluoro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, TfOH (0.1 mL) was slowly added into the solution of N-(1-cyanocyclopropyl)-3-(4-fluoro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (20 mg, 0.03 mmol) in dichloromethane (0.5 mL), and the reaction mixture was stirred at room temperature for 10 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the crude product was purified by pre-HPLC to obtain the title compound (white solid, 0.5 mg, yield: 2.4%). LC/MS (ESI) m/z : 555 $[M+H]^+$.

Example

9:

N-(1-cyanocyclopropyl)-3-(5-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step 1: 3-((tert-butyldimethylsilyl)oxy)-4-chlorobutanenitrile

At 0°C, imidazole (19 g, 281.0 mmol) and tert-butyldimethylchlorosilane (32 g, 210.7 mmol) were slowly added to the solution of 4-chloro-3-hydroxybutyronitrile (24 g, 200.7 mmol) in DMF (200 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred overnight at room temperature under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title compound (colorless oil, 45 g, yield: 95.8%). ¹H NMR (400 MHz, CDCl₃) δ 4.11 - 4.09 (m, 1H), 3.55 - 3.43 (m, 2H), 2.72 - 2.60 (m, 2H), 0.89 (d, *J* = 3.0 Hz, 9H), 0.14 (d, *J* = 3.0 Hz, 3H), 0.11 (d, *J* = 2.9 Hz, 3H).

Step 2: Ethyl 5-((tert-butyldimethylsilyl)oxy)-6-chloro-3-oxohexanoate

3-[(tert-butyldimethylsilyl)oxy]-4-chlorobutyronitrile (20 g, 85.5 mmol) was dissolved in tetrahydrofuran

(200 mL); zinc powder (7.8 g, 119 mmol) and methanesulfonic acid (820 mg, 0.86 mmol) were added to the resulting mixture; the reaction mixture was stirred at 75°C for 10 minutes under an atmosphere of nitrogen; and then, 2-bromo ethyl acetate (11.4 mL, 102.6 mmol) was added. The reaction mixture was continued to be stirred at 75°C for 3 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, poured into ice water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title compound (colorless oil, 25 g, yield: 90.5%).

Step 3: 5-(2-((tert-butyldimethylsilyl)oxy)-3-chloropropyl)-3H-pyrazol-3-one

Hydrazine hydrate (3 mL) was added to the solution of 5-[(tert-butyldimethylsilyl)oxy]-6-chloro-3-oxoethyl caproate (12 g, 37.1 mmol); the reaction mixture was replaced three times with a nitrogen-filled balloon, and then stirred at 65°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (white solid, 8 g, yield: 78.3%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.30 (s, 1H), 4.08 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.59 - 3.54 (m, 1H), 3.52 - 3.48 (m, 1H), 2.72 (dd, *J* = 14.6, 5.7 Hz, 1H), 2.63 (dd, *J* = 14.6, 6.8 Hz, 1H), 0.83 (s, 9H), 0.04 (d, *J* = 2.9 Hz, 3H), -0.07 (s, 3H). LC/MS (ESI) (*m/z*): 289 [M+H]⁺.

Step 4: 5-(2-((tert-butyldimethylsilyl)oxy)-5,6-dihydro-1H-pyrrolo[1,2-*b*]pyrazol-2(4H)-one

At room temperature, cesium carbonate (5.0 g, 15.5 mmol) was added to the solution of 5-(2-((tert-butyldimethylsilyl)oxy)-3-chloropropyl)-1,2-dihydro-3H-pyrazol-3-one (3.8 g, 12.8 mmol) in acetonitrile (70 mL). The reaction mixture was replaced three times with a nitrogen-filled balloon and then stirred at 60°C for 8 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (white solid, 2.5 g, yield: 76.5%). ¹H NMR (400 MHz, CDCl₃) δ 5.26 (s, 1H), 4.86 - 4.81 (m, 1H), 4.06 (dd, *J* = 10.3, 6.4 Hz, 1H), 3.71 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.02 (dd, *J* = 16.2, 7.0 Hz, 1H), 2.64 (dd, *J* = 16.2, 3.8 Hz, 1H), 0.79 (s, 9H), 0.00 (s, 6H). LC/MS (ESI) (*m/z*): 255 [M+H]⁺.

Step 5: 5-(2-((tert-butyldimethylsilyl)oxy)-5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl trifluoromethanesulfonate

At 0°C, triethylamine (1.8 mL, 12.9 mmol) was added to the solution of 5-(2-((tert-butyldimethylsilyl)oxy)-5,6-dihydro-1H-pyrrolo[1,2-*b*]pyrazol-2(4H)-one (1.1 g, 4.3 mmol) in

dichloromethane (10 mL); and then, trifluoromethanesulfonic anhydride (1.1 mL, 6.5 mmol) was dropwise added slowly. The reaction mixture was stirred at room temperature for 1.5 hours. After completion of the reaction, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title compound (colorless oil, 1.3 g, yield: 77.8%). LC/MS (ESI) (m/z): 387 [M+H]⁺.

Step

6:

5-((tert-butyldimethylsilyl)oxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole

At room temperature, bis(pinacolato)diboron (591 mg, 2.3 mmol), potassium acetate (457 mg, 4.6 mmol), XPhos (148 mg, 0.3 mmol) and Pd₂(dba)₃ (142 mg, 0.16 mmol) were sequentially added to the solution of 5-((tert-butyldimethylsilyl)oxy)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl-trifluoromethanesulfonate (600 mg, 1.5 mmol) in 1,4-dioxane (10 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 8 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 400 mg, yield: 70.7%). LC/MS (ESI) (m/z): 365 [M+H]⁺.

Step

7:

3-(5-((tert-butyldimethylsilyl)oxy)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

The title compound was prepared by referring to the preparation method in Step 5 of **Example 7** (white solid, 160 mg, yield: 48.9%). LC/MS (ESI) (m/z): 774 [M+H]⁺.

Step

8:

N-(1-cyanocyclopropyl)-3-(5-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, tetrabutylammonium fluoride (108 mg, 0.4 mmol) was added to the solution of 3-(5-((tert-butyldimethylsilyl)oxy)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (160 mg, 0.2 mmol) in tetrahydrofuran (2 mL); and after the addition, the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, sequentially washed with saturated aqueous ammonium chloride solution and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 50-100% ethyl acetate) to obtain the title compound (white solid, 120 mg, yield: 88%). ¹H NMR (400 MHz, CD₃OD) δ 9.68 (s, 1H), 7.95 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.82 –

6.78 (m, 3H), 6.52 (s, 1H), 5.08 - 5.04 (m, 1H), 4.53 - 4.51 (m, 2H), 4.47 - 4.43 (m, 1H), 4.12 - 4.08 (m, 2H), 3.87 - 3.84 (m, 4H), 3.75 - 3.73 (m, 3H), 3.56 - 3.52 (m, 2H), 3.47 - 3.44 (m, 2H), 3.04 - 2.99 (m, 1H), 2.91 - 2.86 (m, 1H), 1.49 - 1.43 (m, 4H), 1.14 (d, $J = 6.6$ Hz, 6H). LC/MS (ESI) (m/z): 660 $[M+H]^+$.

Step

9:

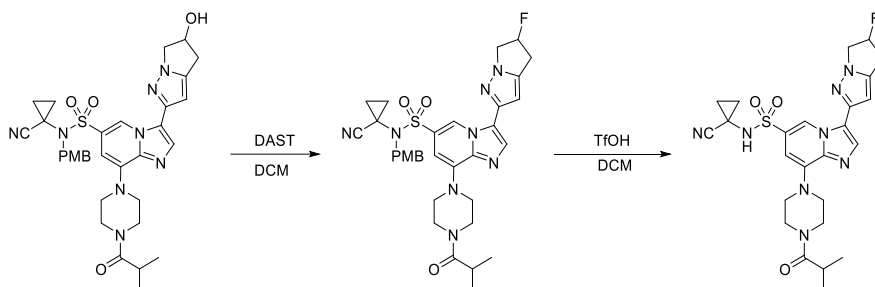
N-(1-cyanocyclopropyl)-3-(5-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

The title compound was prepared by referring to the preparation method in Step 7 of **Example 7** (white solid, 4 mg, yield: 25.4%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.55 (s, 1H), 8.04 (s, 1H), 6.76 (s, 1H), 6.59 (s, 1H), 5.67 - 5.62 (m, 1H), 4.98 - 4.93 (m, 1H), 4.45 - 4.40 (m, 1H), 4.02 - 3.97 (m, 1H), 3.76 - 3.69 (m, 4H), 3.66 - 3.53 (m, 5H), 2.98 - 2.93 (m, 1H), 2.79 - 2.74 (m, 1H), 1.44 - 1.39 (m, 2H), 1.33 - 1.28 (m, 2H), 1.04 (d, $J = 6.3$ Hz, 6H). LC/MS (ESI) (m/z): 539 $[M+H]^+$.

Example

10:

N-(1-cyanocyclopropyl)-3-(5-fluoro-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

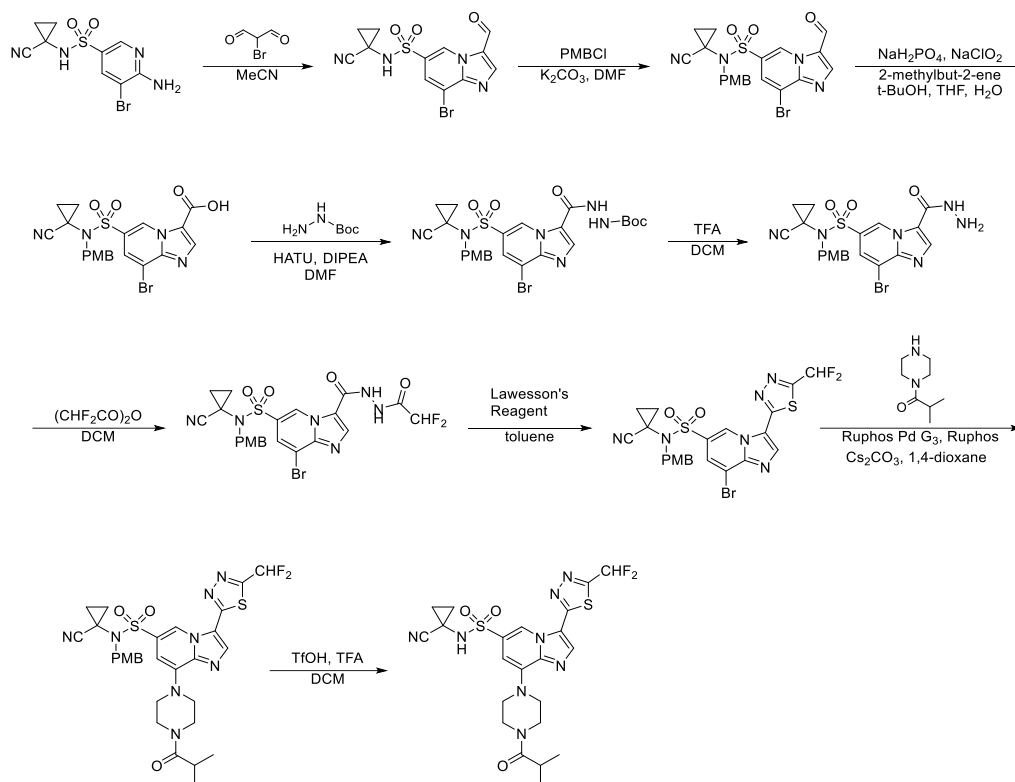


The title compound was prepared by referring to the preparation method in **Example 8** (white solid, 6 mg, yield: 24.4%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.57 (s, 1H), 9.28 (s, 1H), 8.09 (s, 1H), 6.77 (s, 1H), 6.69 (s, 1H), 5.92 (d, $J = 52.3$ Hz, 1H), 4.62 - 4.41 (m, 2H), 3.76 - 3.65 (m, 6H), 3.60 - 3.54 (m, 2H), 3.47 - 3.39 (m, 1H), 3.18 - 3.11 (m, 1H), 2.98 - 2.91 (m, 1H), 1.48 - 1.43 (m, 2H), 1.37 - 1.33 (m, 2H), 1.04 (d, $J = 6.4$ Hz, 6H). LC/MS (ESI) (m/z): 541 $[M+H]^+$.

Example

11:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step 1: 8-bromo-N-(1-cyanocyclopropyl)-3-formylimidazo[1,2-a]pyridine-6-sulfonamide

2-bromomalonialdehyde (710 mg, 4.7 mmol) was slowly added to the solution of 6-amino-5-bromo-N-(1-cyanochloropropyl)pyridin-3-sulfonamide (1.5 g, 4.7 mmol) in acetonitrile (15 mL). The reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 960 mg, yield: 59.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.07 (s, 1H), 9.84 (d, *J* = 1.6 Hz, 1H), 9.60 (s, 1H), 8.76 (s, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 1.54 - 1.47 (m, 2H), 1.40 - 1.35 (m, 2H). LC/MS (ESI) *m/z*: 369 [M+H]⁺.

Step

2:

8-bromo-N-(1-cyanocyclopropyl)-3-formyl-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

K₂CO₃ (1.1 g, 7.8 mmol) and 4-methoxybenzyl chloride (611 mg, 3.9 mmol) was slowly added to the solution of 8-bromo-N-(1-cyanochloropropyl)-3-formylimidazo[1,2-a]pyridin-6-sulfonamide (960 mg, 2.6 mmol) in N,N-dimethylformamide (8 mL). The reaction mixture was stirred at 45°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature; water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the title compound (yellow solid, 800 mg, yield: 62.9%). LC/MS (ESI) *m/z*: 489

[M+H]⁺.

Step

3:

8-bromo-6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)imidazo[1,2-a]pyridine-3-carboxylic acid

At

0°C,

8-bromo-N-(1-cyanocyclopropyl)-3-formyl-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (800 mg, 1.6 mmol) was dissolved in the mixed solution of tertiary butanol (6 mL), tetrahydrofuran (3 mL) and water (2 mL), and sodium dihydrogen phosphate (981 mg, 8.2 mmol), 2-methylbut-2-ene (917 mg, 13.1 mmol) and sodium chlorite (370 mg, 4.1 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: dichloromethane/methanol, gradient: 0-4% methanol) to obtain the title compound (yellow solid, 400 mg, yield: 48.2%). LC/MS (ESI) m/z: 505 [M+H]⁺.

Step

4:

Tert-butyl

2-(8-bromo-6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)imidazo[1,2-a]pyridine-3-carbonyl)hydrazine-1-carboxylate

At room temperature, N,N-diisopropylethylamine (307 mg, 2.38 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (331 mg, 0.87 mmol) were sequentially added to the solution of 8-bromo-6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)imidazo[1,2-a]pyridin-3-carboxylic acid (400 mg, 0.79 mmol) and N'-[(tert-butoxy)carbonyl](tert-butoxy)formylhydrazine (115 mg, 0.87 mmol) in N,N-dimethylformamide (4 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the title compound (yellow solid, 260 mg, yield: 53.1%). LC/MS (ESI) (m/z): 619 [M+H]⁺.

Step

5:

8-bromo-N-(1-cyanocyclopropyl)-3-(hydrazinecarbonyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (1 mL) was slowly added to the solution of 2-(8-bromo-6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)imidazo[1,2-a]pyridin-3-carbonyl)hydrazine-1-tert-butyl carboxylate (260 mg, 0.42 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was

concentrated under reduced pressure to obtain the title compound (yellow oil, 220 mg, yield: 100%). LC/MS (ESI) (m/z): 519 [M+H]⁺.

Step

6:

8-bromo-N-(1-cyanocyclopropyl)-3-(2-(2,2-difluoroacetyl)hydrazine-1-carbonyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, 2,2-difluoroacetyl-2,2-difluoroacetate (62 mg, 0.47 mmol) was dropwise added slowly into the solution of 8-bromo-N-(1-cyanocyclopropyl)-3-(hydrazinocarbonyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (220 mg, 0.42 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 195 mg, yield: 77.1%). LC/MS (ESI) (m/z): 597 [M+H]⁺.

Step

7:

8-bromo-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, the Lawesson's reagent (52 mg, 0.13 mmol) was added to the solution of 8-bromo-N-(1-cyanocyclopropyl)-3-(2-(2,2-difluoroacetyl)hydrazine-1-carbonyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (70 mg, 0.12 mmol) in toluene (1 mL). The reaction mixture was stirred at 110°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-55% ethyl acetate) to obtain the title compound (yellow solid, 35 mg, yield: 50%). LC/MS (ESI) (m/z): 595 [M+H]⁺.

Step

8:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, cesium carbonate (38 mg, 0.12 mmol), RuPhos (5 mg, 0.012 mmol) and RuPhos Pd G3 (5 mg, 0.006 mmol) were added to the solution of 8-bromo-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (35 mg, 0.06 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (18 mg, 0.12 mmol) in 1,4-dioxane (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 110°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction,

the reaction mixture was cooled to room temperature; water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-4% methanol) to obtain the title compound (yellow solid, 24 mg, yield: 60%). LC/MS (ESI) m/z : 671 $[M+H]^+$.

Step

9:

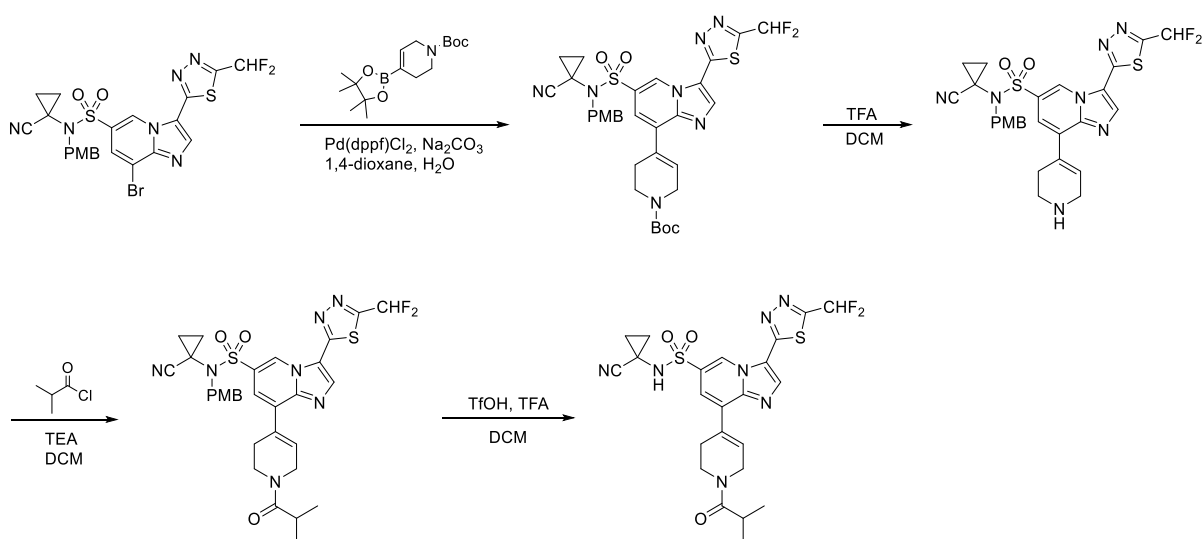
N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (0.5 mL) and trifluoromethanesulfonic acid (0.1 mL) was slowly added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (24 mg, 0.04 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by pre-HPLC (C_{18} , 10-80% acetonitrile in H_2O and 0.1% $HCOOH$) to obtain the title compound (white solid, 3 mg, yield: 15.2%). ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.75 (d, $J = 1.2$ Hz, 1H), 8.66 (s, 1H), 7.70 (t, $J = 53.2$ Hz, 1H), 7.00 (s, 1H), 3.81 - 3.59 (m, 8H), 3.00 - 2.91 (m, 1H), 1.50 - 1.41 (m, 2H), 1.41 - 1.34 (m, 2H), 1.05 (s, 3H), 1.03 (s, 3H). LC/MS (ESI) (m/z): 551 $[M+H]^+$.

Example

12:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(1-isobutyryl-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step

1:

Tert-butyl

4-(6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-

yl)imidazo[1,2-a]pyridin-8-yl)-3,6-dihydropyridine-1(2H)-carboxylate

At room temperature, sodium carbonate (32 mg, 0.30 mmol), N-tert-butoxycarbonyl-1,2,5,6-tetrahydropyridin-4-pinacolboronate (62 mg, 0.20 mmol) and Pd(dppf)Cl₂ (7 mg, 0.01 mmol) were sequentially added to the solution of 8-bromo-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (60 mg, 0.10 mmol) in 1,4-dioxane (2.4 mL) and water (0.4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 90°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, the reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow oil, 65 mg, yield: 92.4%). LC/MS (ESI) (m/z): 698 [M+H]⁺.

Step**2:****N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-8-(1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-6-sulfonamide**

In an ice bath, trifluoroacetic acid (0.4 mL) was slowly added to the solution of 4-(6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridin-8-yl)-3,6-dihydropyridin-1(2H)-tert-butyl carboxylate (65 mg, 0.09 mmol) in dichloromethane (1.2 mL); and the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was directly concentrated to obtain the title compound (yellow oil, 60 mg, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 598 [M+H]⁺.

Step**3:****N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(1-isobutyryl-1,2,3,6-tetrahydropyridin-4-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide**

At 0°C, triethylamine (0.02 mL, 0.16 mmol) and isobutyryl chloride (0.01 mL, 0.12 mmol) were sequentially added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-8-(1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-6-sulfonamide (60 mg, 0.09 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 1 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched by adding water, extracted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the title compound (yellow solid, 35 mg, yield: 56.3%). LC/MS (ESI) (m/z): 668 [M+H]⁺.

Step**4:**

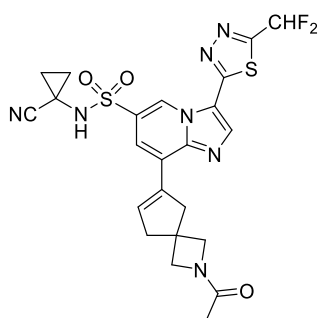
N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(1-isobutyryl-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the synthesis method in Step 11 of **Example 11**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.09 (s, 1H), 9.56 (s, 1H), 8.79 (s, 1H), 7.86 - 7.58 (m, 2H), 7.38 (d, *J* = 29.4 Hz, 1H), 4.33 (d, *J* = 54.7 Hz, 2H), 3.81 (d, 2H), 3.04 - 2.91 (m, 1H), 2.74 (d, *J* = 51.4 Hz, 2H), 1.48 (d, *J* = 4.0 Hz, 2H), 1.40 (d, *J* = 4.6 Hz, 2H), 1.07 (d, *J* = 6.6 Hz, 6H). LC/MS (ESI) (*m/z*): 548 [M+H]⁺.

Example

13:

8-(2-acetyl-2-azaspiro[3.4]oct-6-en-6-yl)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

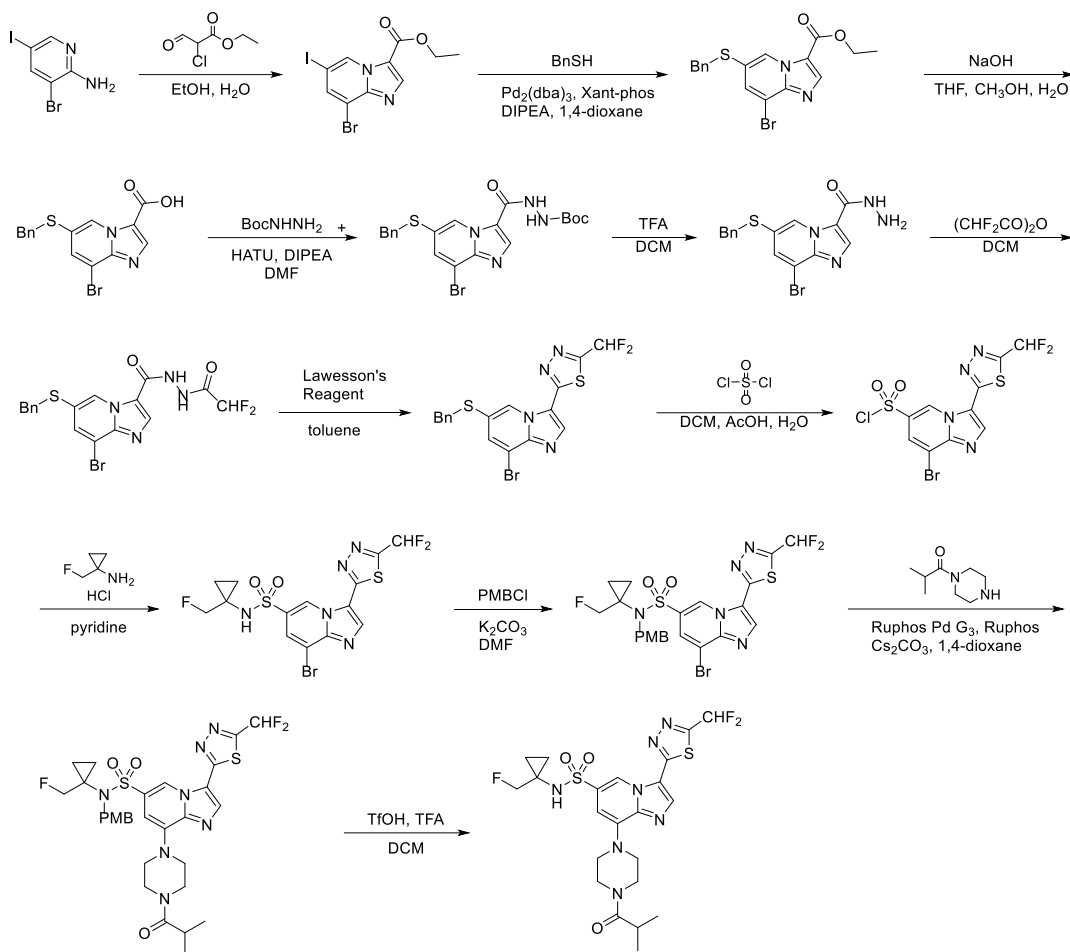


The title compound was prepared by referring to the synthesis method in **Example 12**, using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspirocyclo[3.4]oct-6-ene-2-tert-butyl carboxylate instead of N-tert-butoxycarbonyl-1,2,5,6-tetrahydropyridin-4-pinacolboronate to obtain the target molecules. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.08 (d, *J* = 1.7 Hz, 1H), 8.81 (s, 1H), 7.87 - 7.55 (m, 3H), 4.30 (d, *J* = 8.4 Hz, 1H), 4.18 (d, *J* = 8.3 Hz, 1H), 3.97 (d, *J* = 9.5 Hz, 1H), 3.90 (d, *J* = 9.5 Hz, 1H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.36 (t, 2H), 1.80 (s, 3H), 1.52 - 1.46 (m, 2H), 1.43 - 1.35 (m, 2H). LC/MS (ESI) (*m/z*): 546 [M+H]⁺.

Example

14:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step 1: Ethyl 8-bromo-6-iodoimidazo[1,2-a]pyridine-3-carboxylate

2-chloro-3-oxoethyl propionate (4 g, 13.4 mmol) was dropwise added to the solution of 3-bromo-5-iodopyridin-2-amine (4 g, 13.4 mmol) in ethanol (20 mL) and water (20 mL). The reaction system was stirred overnight at 90°C under an atmosphere of nitrogen. Then, the mixture was cooled to room temperature and filtered, and the filter cake was dried under reduced pressure to obtain target molecules (white solid, 4 g, yield: 75.7%), which were directly used in the next step of reaction. ¹H NMR (400 MHz, CDCl₃) δ 9.54 (d, *J*=1.4 Hz, 1H), 8.21 (s, 1H), 7.84 (d, *J*=1.4 Hz, 1H), 4.45 - 4.32 (m, 2H), 1.39 (t, *J*=7.1 Hz, 3H). LC/MS (ESI) (*m/z*): 395 [M+H]⁺.

Step 2: Ethyl 6-(benzylthio)-8-bromoimidazo[1,2-a]pyridine-3-carboxylate

N,N-diisopropylethylamine (3.9 g, 30.3 mmol) was dropwise added to the solution of 8-bromo-6-iodoimidazol[1,2-a]pyridin-3-ethyl carboxylate (4 g, 10.1 mmol) in 1,4-dioxane (80 mL); and then, under an atmosphere of nitrogen, benzyl mercaptan (1.3 g, 10.1 mmol), XantPhos (579 mg, 1.0 mmol) and Pd₂(dba)₃ (467 mg, 0.51 mmol) were added respectively. The flask was replaced with nitrogen gas three times and then the mixture was stirred at 70°C for 2 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over

anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-15% ethyl acetate) to obtain the title compound (yellow solid, 3.5 g, yield: 88.3%). LC/MS (ESI) (m/z): 393 [M+H]⁺.

Step 3: 6-(benzylthio)-8-bromoimidazo[1,2-a]pyridine-3-carboxylic acid

At 0°C, sodium hydroxide (82 mg, 2.04 mmol) was added to the solution of 6-(benzylthio)-8-bromoimidazo[1,2-a]pyridin-3-ethyl carboxylate (400 mg, 1.02 mmol) in methanol (1.5 mL), tetrahydrofuran (1.5 mL) and water (1.5 mL); and the reaction mixture was stirred at 45°C for one hour. The reaction mixture was diluted with water, acidified to pH-5 with 1N hydrochloric acid, and extracted with ethyl acetate twice. The combined organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain target molecules (yellow solid, 350 mg, yield: 94.3%), which were directly used in the next reaction. LC/MS (ESI) (m/z): 365 [M+H]⁺.

Step

4:

Tert-butyl

2-(6-(benzylthio)-8-bromoimidazo[1,2-a]pyridine-3-carbonyl)hydrazine-1-carboxylate

N,N-diisopropylethylamine (373 mg, 2.89 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (403 mg, 1.06 mmol) were sequentially added to the solution of 6-(benzylthio)-8-bromoimidazo[1,2-a]pyridin-3-carboxylic acid (350 mg, 0.96 mmol) and tert-butyl hydrazinofomate (127 mg, 0.96 mmol) in DMF (4 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 440 mg, yield: 95.7%). LC/MS (ESI) (m/z): 479 [M+H]⁺.

Step 5: 6-(benzylthio)-8-bromoimidazo[1,2-a]pyridine-3-carbohydrazide

At 0°C, trifluoroacetic acid (1 mL) was dropwise added to the solution of 2-(6-(benzylthio)-8-bromoimidazo[1,2-a]pyridin-3-carbonyl)hydrazin-1-tert-butyl carboxylate (440 mg, 0.92 mmol) in dichloromethane (3 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was and concentrated under reduced pressure to obtain a crude target product (yellow oil, 348 mg, yield: 100%), which was directly used in the next reaction. LC/MS (ESI) (m/z): 379 [M+H]⁺.

Step 6: 6-(benzylthio)-8-bromo-N'-(2,2-difluoroacetyl)imidazo[1,2-a]pyridine-3-carbohydrazide

At 0°C, 2,2-difluoroacetyl-2,2-difluoroacetate (160 mg, 0.92 mmol) was dropwise added to the solution of 6-(benzylthio)-8-bromoimidazo[1,2-a]pyridin-3-formylhydrazine (348 mg, 0.92 mmol) in dichloromethane (4 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution and saturated brine respectively, dried over anhydrous sodium sulfate, filtered and concentrated to

dryness. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the target product (yellow solid, 350 mg, yield: 83.3%). LC/MS (ESI) (m/z): 457 [M+H]⁺.

Step 7: 2-(6-(benzylthio)-8-bromoimidazo[1,2-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

Under an atmosphere of nitrogen, the Lawesson's reagent (326 mg, 0.81 mmol) was added to the solution of 6-(benzylthio)-8-bromo-N'-(2,2-difluoroacetyl)imidazo[1,2-a]pyridin-3-carbohydrazide (350 mg, 0.77 mmol) in toluene (4 mL); the flask was replaced with nitrogen gas three times and then the mixture was stirred at 110°C for 2 hours under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the target product (yellow solid, 310 mg, yield: 89%). LC/MS (ESI) (m/z): 455 [M+H]⁺.

Step 8: 8-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonyl chloride

At 0°C, acetic acid (0.1 mL) and water (0.05 mL) were sequentially added to the solution of 2-(6-(benzylthio)-8-bromoimidazo[1,2-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (310 mg, 0.68 mmol) in dichloromethane (3 mL); then, sulfonyl chloride (369 mg, 2.74 mmol) was dropwise added slowly; and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with dichloromethane, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a crude target product (yellow oil, 294 mg, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 431 [M+H]⁺.

Step 9: 8-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, 8-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonyl chloride (294 mg, 0.68 mmol) was added to the solution of 1-(fluoromethyl)cyclopropyl-1-amine hydrochloride (172 mg, 1.37 mmol) in pyridine (3 mL); and then, the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0 - 45% ethyl acetate) to obtain target molecules (yellow solid, 100 mg, yield: 30.3%). LC/MS (ESI) m/z: 484 [M+H]⁺.

Step 10: 8-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

Potassium carbonate (86 mg, 0.63 mmol) and 1-(chloromethyl)-4-methoxybenzene (49 mg, 0.31 mmol) were sequentially added to the solution of

8-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)imidazo[1,2-a]pyridin-6-sulfonamide (100 mg, 0.21 mmol) in N,N- (2 mL); and the reaction mixture was stirred at 45°C for 2 hours. The mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the target product (yellow solid, 75 mg, yield: 60%). LC/MS (ESI) m/z: 604 [M+H]⁺.

Step

11:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, 2-methyl-1-(piperazin-1-yl)propan-1-one (39 mg, 0.25 mmol), cesium carbonate (81 mg, 0.25 mmol), RuPhos (12 mg, 0.02 mmol) and RuPhos Pd G3 (10 mg, 0.01 mmol) were sequentially added to the solution of 8-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (75 mg, 0.12 mmol) in 1,4-dioxane (2 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 100°C for 3 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate, and filtered; the filtrate was concentrated under reduced pressure; and the residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-75% ethyl acetate) to obtain the target product (yellow solid, 60 mg, yield: 71.1%). LC/MS (ESI) m/z: 678 [M+H]⁺.

Step

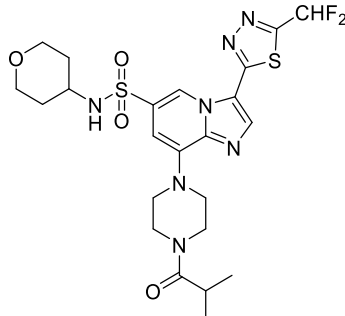
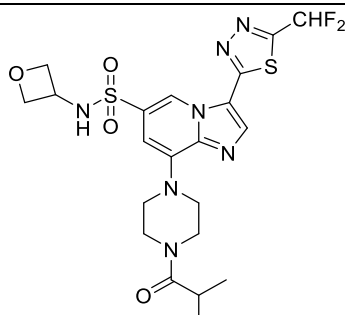
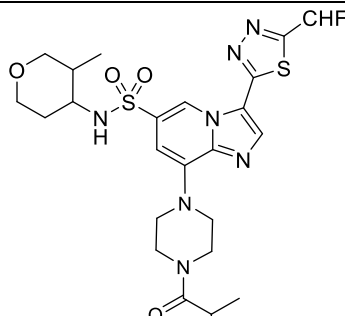
12:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (0.5 mL) and trifluoromethanesulfonic acid (0.1 mL) were sequentially added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (60 mg, 0.09 mmol) in dichloromethane (0.5 mL); and then, the reaction mixture was stirred at room temperature for 30 minutes. The mixture was concentrated to dryness, and the residue was purified by pre-HPLC to obtain target molecules (white solid, 16 mg, yield: 32.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 1H), 8.79 (s, 1H), 8.61 (s, 1H), 7.83 - 7.51 (m, 1H), 7.00 (s, 1H), 4.27 (s, 1H), 4.15 (s, 1H), 3.67 (dd, *J* = 50.5, 26.4 Hz, 8H), 2.95 (dt, *J* = 13.4, 6.6 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 6H), 0.85 - 0.80 (m, 2H), 0.80 - 0.74 (m, 2H). LC/MS (ESI) (m/z): 558 [M+H]⁺.

By referring to the preparation method in Example 14, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude

product to obtain the title compound.

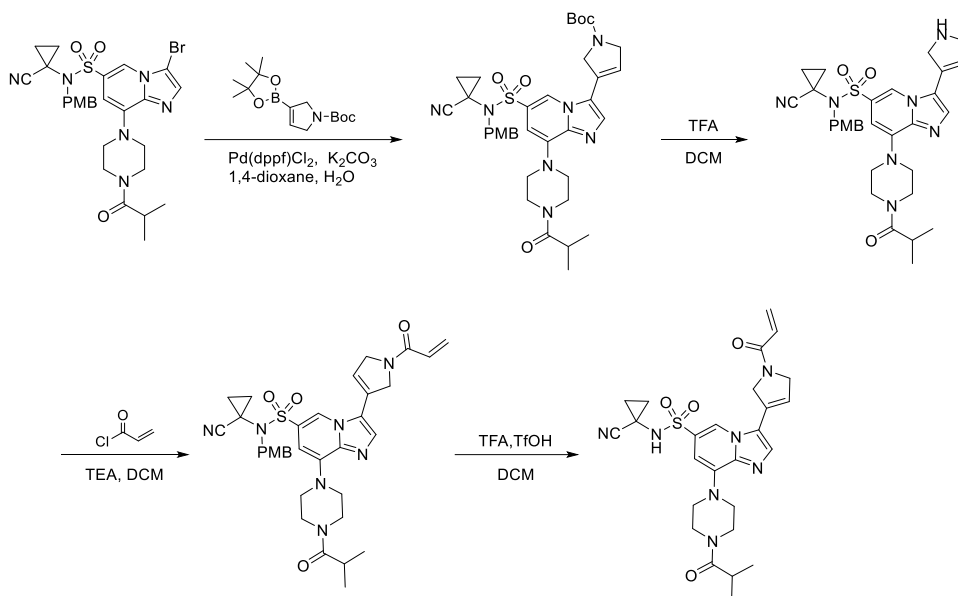
Example	Structure and name	Analysis data
Example 15	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (d, <i>J</i> = 1.3 Hz, 1H), 8.63 (s, 1H), 8.15 (d, <i>J</i> = 7.1 Hz, 1H), 7.64 (t, <i>J</i> = 53.0 Hz, 1H), 7.07 (d, <i>J</i> = 1.3 Hz, 1H), 3.78 - 3.66 (m, 8H), 3.58 (s, 2H), 3.28 - 3.20 (m, 3H), 3.00 - 2.93 (m, 1H), 1.61 (d, <i>J</i> = 10.5 Hz, 2H), 1.45 - 1.37 (m, 2H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 570 [M+H] ⁺ .
Example 16	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(oxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.61 (d, <i>J</i> = 1.4 Hz, 1H), 8.92 (d, <i>J</i> = 7.7 Hz, 1H), 8.64 (s, 1H), 7.71 (t, <i>J</i> = 53.2 Hz, 1H), 6.96 (d, <i>J</i> = 1.3 Hz, 1H), 4.58 - 4.52 (m, 2H), 4.51 - 4.43 (m, 1H), 4.38 - 4.32 (m, 2H), 3.79 - 3.58 (m, 8H), 3.00 - 2.93 (m, 1H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 542 [M+H] ⁺ .
Example 17	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyltetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (d, <i>J</i> = 1.4 Hz, 1H), 8.63 (s, 1H), 8.09 (d, <i>J</i> = 7.5 Hz, 1H), 7.70 (t, <i>J</i> = 53.2 Hz, 1H), 7.10 (d, <i>J</i> = 1.4 Hz, 1H), 3.80 - 3.53 (m, 12H), 3.45 - 3.42 (m, 1H), 2.98 - 2.93 (m, 1H), 1.81 - 1.73 (m, 1H), 1.51 - 1.39 (m, 2H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H), 0.79 (d, <i>J</i> = 7.0 Hz, 3H). LC/MS (ESI) (<i>m/z</i>): 584 [M+H] ⁺ .

	fonamide	
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Example

18:

3-(1-acryloyl-2,5-dihydro-1H-pyrrol-3-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide



Step

1:

Tert-butyl

3-(6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate

At room temperature, potassium carbonate (67 mg, 0.48 mmol) and Pd(dppf)Cl₂ (11 mg, 0.02 mmol) were sequentially added to the mixed solution of 3-bromo-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide (100 mg, 0.16 mmol), 1-tert-butoxycarbonyl-2,5-dihydro-1H-pyrrolo-3-pinacolboronate (65 mg, 0.21 mmol) in 1,4-dioxane (3 mL) and water (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-55% ethyl acetate) to obtain the target product (white solid, 80 mg, yield: 69.9%). LC/MS (ESI) (m/z): 704 [M+H]⁺.

Step

2:

N-(1-cyanocyclopropyl)-3-(2,5-dihydro-1H-pyrrol-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (1 mL) was dropwise added slowly to the solution of

3-(6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2,5-dihydro-1H-pyrrolo-1-tert-butyl carboxylate (80 mg, 0.11 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 1.5 hours. After completion of the reaction, the reaction mixture was directly concentrated under reduced pressure to obtain a crude title compound (yellow oil, 80 mg, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 604 [M+H]⁺.

Step

3:

3-(1-acryloyl-2,5-dihydro-1H-pyrrol-3-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, TEA (0.1 mL, 0.3 mmol) and acryloyl chloride (0.01 mL, 0.15 mmol) were dropwise added to the solution of

N-(1-cyanocyclopropyl)-3-(2,5-dihydro-1H-pyrrolo-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide trifluoroacetate (80 mg, 0.11 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 1.5 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-50% ethyl acetate) to obtain the target product (white solid, 40 mg, yield: 61.19%). LC/MS (ESI) (m/z): 658 [M+H]⁺.

Step

4:

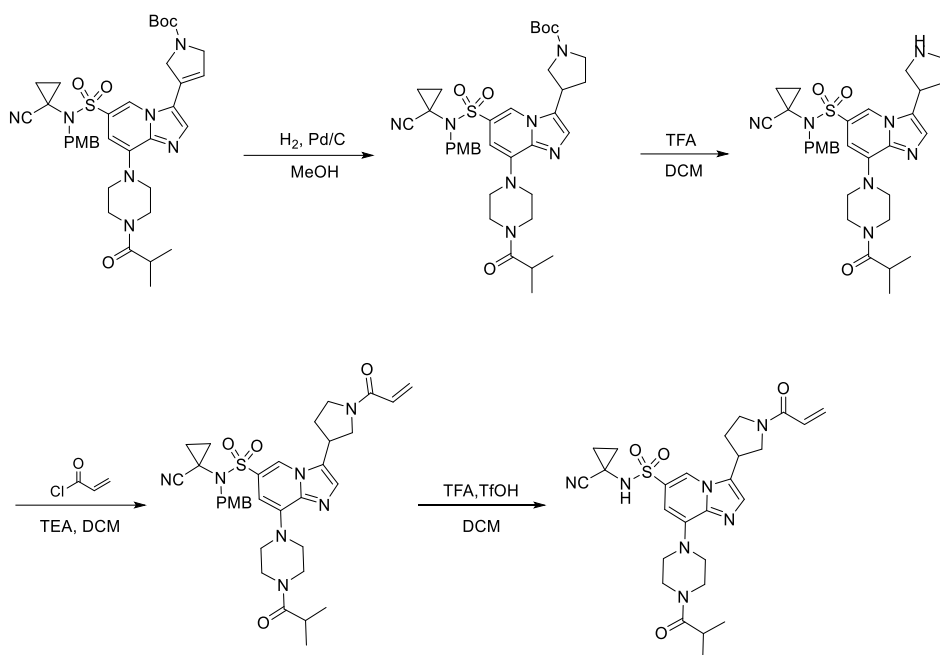
3-(1-acryloyl-2,5-dihydro-1H-pyrrol-3-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (0.05 mL) and trifluoromethanesulfonic acid (0.05 mL) were dropwise added slowly to the solution of 3-(1-acryloyl-2,5-dihydro-1H-pyrrolo-3-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,2-a]pyridin-6-sulfonamide (40 mg, 0.06 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at 0°C for 2 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the residue was purified by pre-HPLC to obtain the title compound (white solid, 12 mg, yield: 36.7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.34 (s, 1H), 8.59 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.88 (d, *J* = 26.9 Hz, 1H), 6.80 (s, 1H), 6.74 - 6.62 (m, 1H), 6.39 (s, 1H), 6.25 (dd, *J* = 16.8, 2.2 Hz, 1H), 5.81 - 5.75 (m, 1H), 4.96 - 4.86 (m, 1H), 4.70 (d, *J* = 9.4 Hz, 2H), 4.51 - 4.46 (m, 1H), 3.77 - 3.66 (m, 6H), 3.60 - 3.55 (m, 2H), 2.98 - 2.93 (m, 1H), 1.51 - 1.46 (m, 2H), 1.39 - 1.35 (m, 2H), 1.04 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 538 [M+H]⁺.

Example

19:

3-(1-acryloylpyrrolidin-3-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide



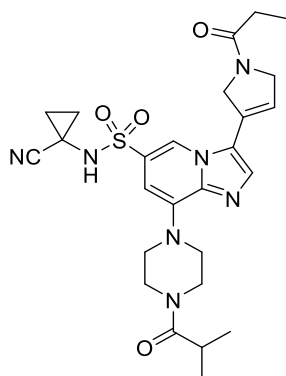
Step 1: **3-{6-[(1-cyanocyclopropyl)(4-methoxyphenyl)methyl]sulfamoyl}-8-[4-(2-methylpropionyl)piperazin-1-yl]imidazo[1,2-a]pyridin-3-yl}pyrrolidin-1-tert-butyl carboxylate**

Under an atmosphere of nitrogen, Pd/C (12 mg, mass fraction: 10%) was slowly added to the solution of 3-(6-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)-2,5-dihydro-1H-pyrrolo-1-tert-butyl carboxylate (80 mg, 0.11 mmol) in methanol (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred for 9 hours at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (white solid, 78 mg, yield: 95.8%). LC/MS (ESI) m/z : 706 $[M+H]^+$.

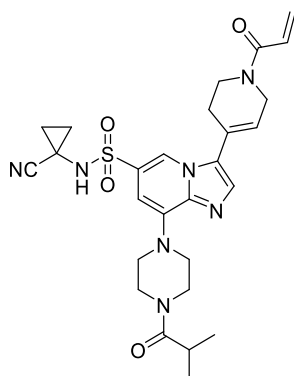
Step 2-4: **3-(1-acryloylpyrrolidin-3-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide**

The title compound was prepared by referring to the synthesis methods in Steps 2-4 of **Example 18** (white solid, yield: 36.7%). ^1H NMR (400 MHz, DMSO- d_6) δ 9.24 (d, $J = 7.0$ Hz, 1H), 8.54 - 8.46 (m, 1H), 7.57 (d, $J = 7.9$ Hz, 1H), 6.69 - 6.67 (m, 1H), 6.67 - 6.58 (m, 1H), 6.21 - 6.13 (m, 1H), 5.73 - 5.65 (m, 1H), 4.19 - 3.88 (m, 2H), 3.83 - 3.63 (m, 8H), 3.59 - 3.53 (m, 2H), 3.50 - 3.42 (m, 1H), 2.98 - 2.91 (m, 1H), 2.46 - 2.31 (m, 1H), 2.15 - 2.01 (m, 1H), 1.49 - 1.43 (m, 2H), 1.41 - 1.34 (m, 2H), 1.04 (d, $J = 6.7$ Hz, 6H). LC/MS (ESI) (m/z): 540 $[M+H]^+$.

Example 20: **N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(1-propionyl-2,5-dihydro-1H-pyrrol-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide**

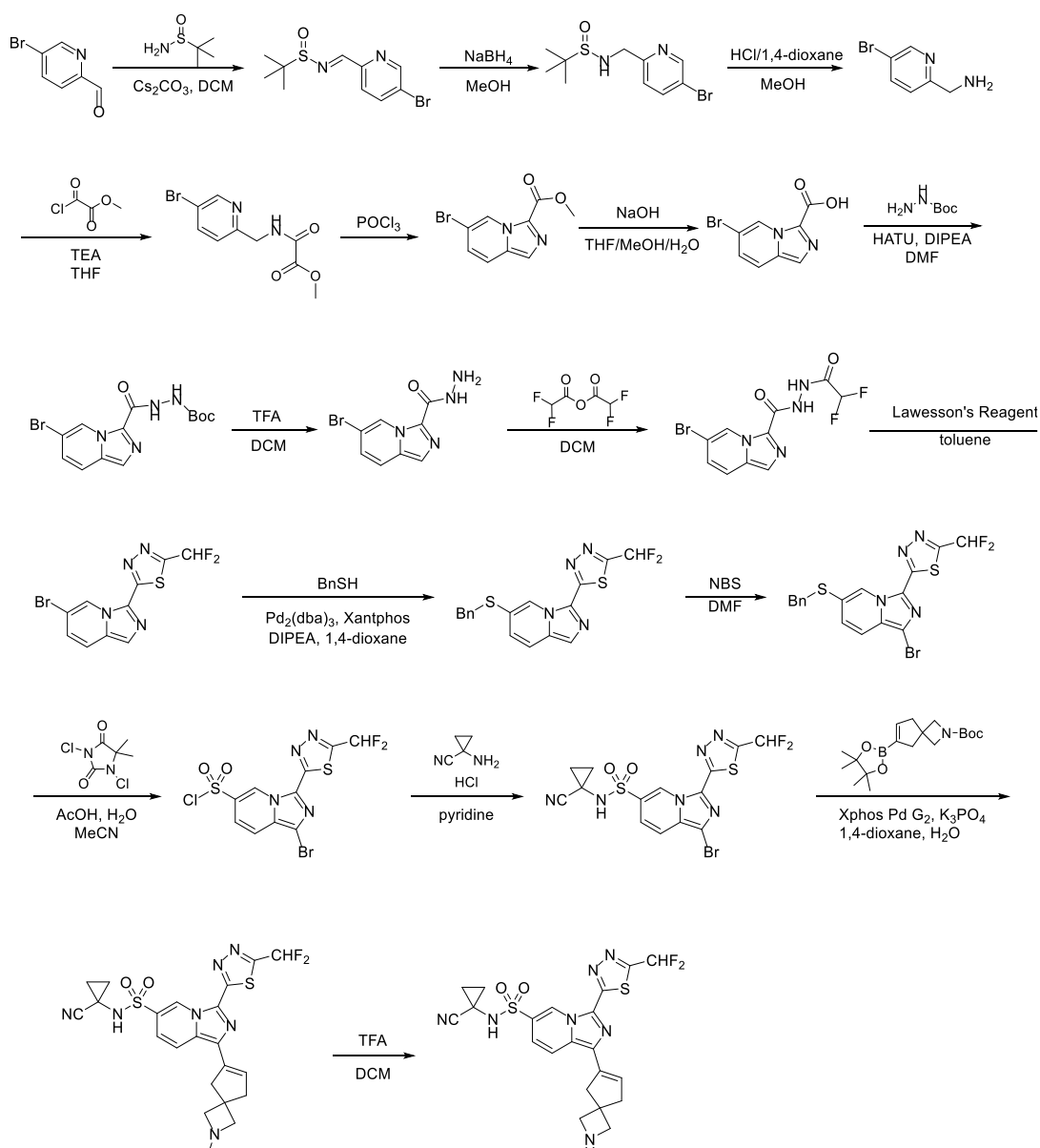
azo[1,2-a]pyridine-6-sulfonamide

The title compound was prepared by referring to the synthesis methods in Step 3-4 of **Example 18**, using propionyl chloride instead of acryloyl chloride (white solid, yield: 20.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (d, *J* = 5.1 Hz, 1H), 7.84 (d, *J* = 22.2 Hz, 1H), 6.79 (s, 1H), 6.36 (s, 1H), 4.76 (s, 1H), 4.58 (s, 2H), 4.40 (s, 1H), 3.79 - 3.68 (m, 4H), 3.66 - 3.54 (m, 4H), 2.96 - 2.89 (m, 1H), 2.40 - 2.33 (m, 2H), 1.43 (s, 2H), 1.35 - 1.29 (m, 2H), 1.08 - 1.02 (m, 9H). LC/MS (ESI) (*m/z*): 540 [M+H]⁺.

Example**21:**
3-(1-acryloyl-1,2,3,6-tetrahydropyridin-4-yl)-N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide


The title compound was prepared by referring to the synthesis method in **Example 18**, using N-tert-butoxycarbonyl-3,6-dihydro-2H-pyridin-4-pinacolboronate instead of 1-tert-butoxycarbonyl-2,5-dihydro-1H-pyrrolo-3-pinacolboronate (white solid, yield: 28.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.28 (s, 1H), 8.48 (s, 1H), 7.73 (s, 1H), 6.98 - 6.81 (m, 1H), 6.70 (s, 1H), 6.25 - 6.14 (m, 2H), 5.80 - 5.70 (m, 1H), 4.44 - 4.25 (m, 2H), 3.90 - 3.79 (m, 2H), 3.76 - 3.66 (m, 4H), 3.66 - 3.52 (m, 4H), 2.98 - 2.91 (m, 1H), 2.64 - 2.54 (m, 2H), 1.51 - 1.44 (m, 2H), 1.39 - 1.33 (m, 2H), 1.04 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (*m/z*): 552 [M+H]⁺.

Example**22:**
N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-(2-azaspiro[3.4]oct-6-en-6-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: N-((5-bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide

At room temperature, cesium carbonate (21 g, 64.5 mmol) and tert-butylsulfinamide (6.5 g, 53.8 mmol) were sequentially added to the solution of 5-bromo-2-pyridylaldehyde (10 g, 53.7 mmol) in dichloromethane (110 mL). The reaction mixture was stirred at 40°C for one hour. After completion of the reaction, the reaction mixture was cooled to room temperature, and quenched by adding ice water. The mixture was extracted with dichloromethane twice; and the organic phase were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-15% ethyl acetate) to obtain the title compound (white solid, 12 g, yield: 77.2%). LC/MS (ESI) (m/z): 289 [M+H]⁺.

Step 2: N-((5-bromopyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide

In an ice bath, sodium borohydride (2.1 g, 62.2 mmol) was added portionwise to the solution of

N-((5-bromopyridin-2-yl)methylene)-2-methylpropan-2-sulfenamide (12 g, 41.5 mmol) in methanol (120 mL); and then, the reaction mixture was stirred at 30°C for 30 minutes. After completion of the reaction, the reaction mixture was quenched with saturated aqueous ammonium chloride solution in an ice bath, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-20% ethyl acetate) to obtain the title compound (yellow liquid, 10.5 g, yield: 86.9%). ¹H NMR (400 MHz, CDCl₃) δ 8.61 (d, *J* = 2.2 Hz, 1H), 7.79 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.28 - 7.26 (s, 1H), 4.42 - 4.36 (m, 2H), 4.18 (t, *J* = 5.6 Hz, 1H), 1.26 (s, 9H). LC/MS (ESI) (m/z): 291 [M+H]⁺.

Step 3: (5-bromopyridin-2-yl)methylamine

In an ice water bath, the solution of hydrochloric acid/1,4-dioxane (50 mL, 4 M) was slowly added to the solution of N-((5-bromopyridin-2-yl)methyl)-2-methylpropan-2-sulfenamide (12 g, 64.5 mmol) in methanol (120 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the saturated aqueous sodium bicarbonate solution was added for neutralization, and the resulting mixture was directly concentrated under reduced pressure. The residue was purified by column chromatography (eluent: dichloromethane/methanol, gradient: 10-20% methanol) to obtain the title compound (white solid, 4.5 g, yield: 70.0%). ¹H NMR (400 MHz, CDCl₃) δ 8.61 (d, *J* = 2.1 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 3.94 (s, 2H). LC/MS (ESI) (m/z): 187 [M+H]⁺.

Step 4: Methyl 2-(((5-bromopyridin-2-yl)methyl)amino)-2-oxoacetate

At 0°C, triethylamine (5 mL, 36 mmol) was added to the solution of (5-bromopyridin-2-yl)methylamine (4.5 g, 24 mmol) in anhydrous tetrahydrofuran (45 mL); and then, methyl oxalyl chloride (2.4 mL, 26.5 mmol) was dropwise added slowly. The reaction mixture was stirred at room temperature for 1 hours. After completion of the reaction, ice water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow solid, 4.5 g, yield: 68.4%). LC/MS (ESI) (m/z): 273 [M+H]⁺.

Step 5: Methyl 6-bromoimidazo[1,5-a]pyridine-3-carboxylate

At room temperature, 2-(((5-bromopyridin-2-yl)methyl)amino)-2-methyl oxyacetate (4.5 g, 16.5 mmol) was added portionwise to phosphorus oxychloride (45 mL); and the reaction mixture was stirred at 110°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the residue was added to the saturated aqueous sodium bicarbonate solution for neutralization, and then extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 30-50% ethyl acetate) to obtain the title compound (yellow solid, 3.0 g, yield: 71.3%). ¹H NMR (400 MHz, CDCl₃) δ 9.53

(s, 1H), 7.64 (s, 1H), 7.54 (d, $J = 9.4$ Hz, 1H), 7.15 (dd, $J = 9.4, 1.3$ Hz, 1H), 4.03 (s, 3H). LC/MS (ESI) (m/z): 255 $[M+H]^+$.

Step 6: 6-bromoimidazo[1,5-a]pyridine-3-carboxylic acid

At room temperature, 6-bromoimidazo[1,5-a]pyridin-3-methyl carboxylate (3 g, 11.8 mmol) was dissolved in the mixed solution of methanol (15 mL), tetrahydrofuran (15 mL) and water (15 mL); and then, sodium hydroxide (520 mg, 12.9 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was adjusted to the pH value of 6 by using 3N hydrochloric acid, and then concentrated under reduced pressure. The residue was purified by column chromatography (eluent: dichloromethane/methanol, gradient: 0-20% methanol) to obtain the title compound (white solid, 2.8 g, yield: 98.7%). LC/MS (ESI) (m/z): 241 $[M+H]^+$.

Step 7: Tert-butyl 2-(6-bromoimidazo[1,5-a]pyridine-3-carbonyl)hydrazine-1-carboxylate

At room temperature, N,N-diisopropylethylamine (5.7 mL, 34.8 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (6.6 g, 17.4 mmol) were sequentially added to the solution of 6-bromoimidazo[1,5-a]pyridin-3-carboxylic acid (2.8 g, 11.6 mmol) and tert-butyl hydrazinoformate (4.8 g, 12.8 mmol) in N,N-dimethylformamide (30 mL). The reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (white solid, 2 g, yield: 48.4%). LC/MS (ESI) (m/z): 355 $[M+H]^+$.

Step 8: 6-bromoimidazo[1,5-a]pyridine-3-carbohydrazide

At 0°C, trifluoroacetic acid (5 mL) was slowly added to the solution of 2-(6-bromoimidazo[1,5-a]pyridin-3-carbonyl)hydrazin-1-tert-butyl carboxylate (2 g, 5.63 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at 25°C for one hour. After completion of the reaction, the reaction mixture was concentrated to obtain a crude title compound (yellow liquid, 1.9 g, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 255 $[M+H]^+$.

Step 9: 6-bromo-N'-(2,2-difluoroacetyl)imidazo[1,5-a]pyridine-3-carbohydrazide

At 0°C, 2,2-difluoroacetyl 2,2-difluoroacetate (0.7 mL, 5.64 mmol) was dropwise added slowly to the solution of 6-bromoimidazo[1,5-a]pyridin-3-carbohydrazide trifluoroacetate (1.9 g, 5.63 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was washed with saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 1.0 g, yield: 65.1%). LC/MS (ESI) (m/z): 333 $[M+H]^+$.

Step 10: 2-(6-bromoimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

At room temperature, the Lawesson's reagent (1.4 g, 3.37 mmol) was added to the solution of 6-bromo-N'-(2,2-difluoroacetyl)imidazo[1,5-a]pyridin-3-carbohydrazide (1 g, 3.06 mmol) in toluene (10 mL). The reaction mixture was stirred at 110°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-55% ethyl acetate) to obtain the title compound (yellow liquid, 676 mg, yield: 66.6%). LC/MS (ESI) (m/z): 331 [M+H]⁺.

Step 11: 2-(6-(benzylthio)imidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

At room temperature, N,N-diisopropylethylamine (1 mL, 6.12 mmol), XantPhos (236 mg, 0.41 mmol), Pd₂(dba)₃ (187 mg, 0.20 mmol), benzyl mercaptane (0.4 mL, 3.06 mmol) were sequentially added to the solution of 2-(6-bromoimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (676 mg, 2.04 mmol) in anhydrous dioxane (7 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 100 °C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow liquid, 700 mg, yield: 91.5%). LC/MS (ESI) (m/z): 375 [M+H]⁺.

Step 12: 2-(6-(benzylthio)-1-bromoimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

At 0°C, N-bromosuccinimide (366 mg, 2.06 mmol) was slowly added to the solution of 2-(6-(benzylthio)imidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (700 mg, 1.87 mmol) in N,N-dimethylformamide (7 mL). The reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, ice water was added for quenching, and the reaction mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-55% ethyl acetate) to obtain the title compound (yellow solid, 800 mg, yield: 94.4%). LC/MS (ESI) (m/z): 453 [M+H]⁺.

Step 13: 1-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride

At 0°C, acetic acid (0.12 mL, 1.98 mmol) was added to the solution of 2-(6-(benzylthio)-1-bromoimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (450 mg, 0.99 mmol) in acetonitrile (10 mL); and then, dichlorohydantoin (489 mg, 2.48 mmol) was added portionwise. The reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium

sulfate, and concentrated under reduced pressure to obtain the title compound (yellow solid, 350 mg, yield: 82.1%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 429 [M+H]⁺.

Step

14:

1-bromo-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, 1-bromo-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride (350 mg, 0.81 mmol) was added portionwise to the solution of 1-amido-1-cyclopropyl cyanic hydrochloride (193 mg, 1.63 mmol) in pyridine (7 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, ice water was added for quenching; the reaction mixture was extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 230 mg, yield: 59.4%). LC/MS (ESI) (m/z): 475 [M+H]⁺.

Step

15:

Tert-butyl

6-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-1-yl)-2-azaspiro[3.4]oct-6-ene-2-carboxylate

At room temperature, potassium phosphate (205 mg, 0.96 mmol) and Xphos Pd G2 (76 mg, 0.10 mmol) were added to the mixed solution of 1-bromo-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonamide (230 mg, 0.48 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxoboracyclopentan-2-yl)-2-azaspirocyclo[3.4]octan-6-ene-2-tert-butyl carboxylate (162 mg, 0.48 mmol) in 1,4-dioxane (18 mL) and water (4.5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether, gradient: 0-55% ethyl acetate) to obtain the title compound (yellow solid, 210 mg, yield: 71.9%). LC/MS (ESI) (m/z): 604 [M+H]⁺.

Step

16:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-(2-azaspiro[3.4]oct-6-en-6-yl)imidazo[1,5-a]pyridine-6-sulfonamide

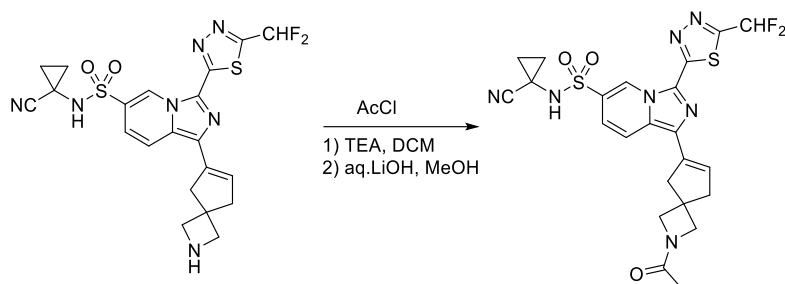
At 0°C, trifluoroacetic acid (0.2 mL) was slowly added to the solution of 6-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-1-yl)-2-azaspiro[3.4]octan-6-ene-2-tert-butyl carboxylate (30 mg, 0.05 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at 25°C for one hour under an atmosphere of nitrogen. After completion of

the reaction, the reaction mixture was concentrated under reduced pressure, and the residue was treated by pre-HPLC (C₁₈, 10-50% acetonitrile in water (containing 0.1% formic acid)) to obtain the title compound (white solid, 8 mg, yield: 32%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.90 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 8.17-8.15 (m, 1H), 7.63 (t, *J* = 53.1 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 6.67 (s, 1H), 3.90-4.15 (m, 5H), 2.97 - 2.90 (m, 2H), 2.39 - 2.33 (m, 2H), 1.32 - 1.25 (m, 2H), 1.21 - 1.14 (m, 2H). LC/MS (ESI) (*m/z*): 504 [M+H]⁺.

Example

23:

1-(2-acetyl-2-azaspiro[3.4]oct-6-en-6-yl)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

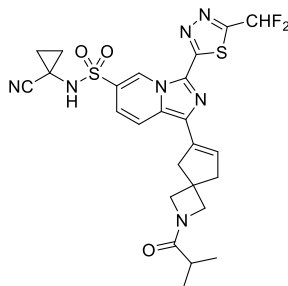


At 0°C, triethylamine (0.04 mL, 0.26 mmol) and acetyl chloride (0.006 mL, 0.09 mmol) were added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-(2-azaspiro[3.4]octan-6-ene-6-yl)imidazo[1,5-a]pyridine-6-sulfonamide (43 mg, 0.09 mmol) in anhydrous dichloromethane (1 mL) respectively. The reaction mixture was stirred at room temperature for 10 minutes. After completion of the reaction, ice water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The concentrated product was dissolved in methanol (1 mL); and then, aqueous lithium hydroxide solution (0.3 mL, 0.3 mmol, 1M) was added. The reaction mixture was stirred at room temperature for 10 minutes, concentrated under reduced pressure, and then purified by pre-HPLC (C₁₈, 10-50% acetonitrile in water (containing 0.1% formic acid)) to obtain the title compound (white solid, 16.9 mg, yield: 36.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.99 (s, 1H), 9.65 (s, 1H), 8.37 (d, *J* = 9.6 Hz, 1H), 7.76 (t, *J* = 53.2 Hz, 1H), 7.41 (dd, *J* = 9.6, 1.3 Hz, 1H), 6.68 (s, 1H), 4.25 (d, *J* = 8.3 Hz, 1H), 4.15 (d, *J* = 8.3 Hz, 1H), 3.98 (d, *J* = 9.5 Hz, 1H), 3.87 (d, *J* = 9.5 Hz, 1H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.34-2.29 (m, 2H), 1.79 (s, 3H), 1.52-1.47 (m, 2H), 1.38-1.34 (m, 2H). LC/MS (ESI) (*m/z*): 546 [M+H]⁺.

Example

24:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-(2-isobutyryl-2-azaspiro[3.4]oct-6-en-6-yl)imidazo[1,5-a]pyridine-6-sulfonamide

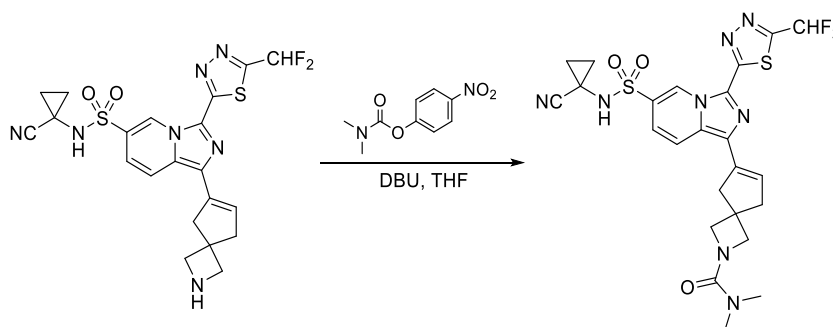


The title compound was prepared by referring to the synthesis method in **Example 23**, using isobutryl chloride instead of acetyl chloride. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.00 (s, 1H), 9.67 (s, 1H), 8.38 (d, *J* = 9.6 Hz, 1H), 7.69 (t, *J* = 54.4, 52.0 Hz, 1H), 7.41 (d, *J* = 9.6 Hz, 1H), 6.70 (s, 1H), 4.29 (d, *J* = 8.1 Hz, 1H), 4.20 (d, *J* = 8.2 Hz, 1H), 3.99 (d, *J* = 9.3 Hz, 1H), 3.88 (d, *J* = 9.4 Hz, 1H), 2.99 - 2.94 (m, 2H), 2.49 - 2.44 (m, 1H), 2.37 - 2.30 (m, 2H), 1.52 - 1.48 (m, 2H), 1.39 - 1.35 (m, 2H), 1.03 - 0.99 (m, 6H). LC/MS (ESI) (*m/z*): 574 [M+H]⁺.

Example

25:

6-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-1-yl)-N,N-dimethyl-2-azaspiro[3.4]oct-6-ene-2-carboxamide

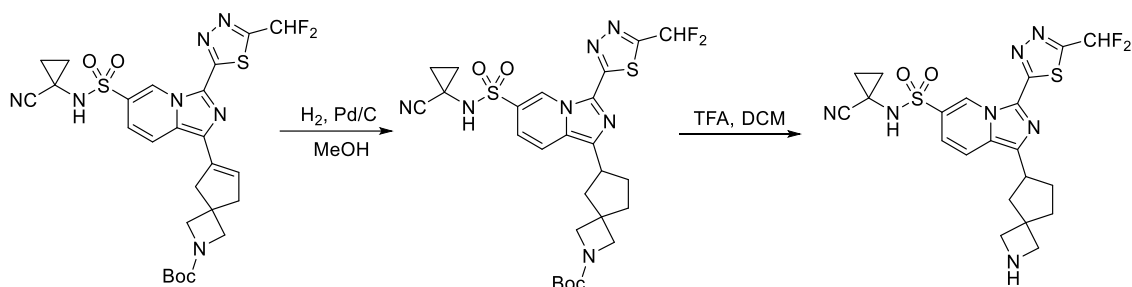


At 0°C, 4-nitrophenyldimethyl carbamate (33 mg, 0.16 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (36 mg, 0.24 mmol) were slowly added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-(2-azaspiro[3.4]octan-6-ene-6-yl)imidazo[1,5-a]pyridin-6-sulfonamide (40 mg, 0.079 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at 80°C for one hour. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium carbonate solution and saturated brine respectively, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (white solid, 5.5 mg, yield: 12.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.98 (s, 1H), 8.37 (d, *J* = 9.1 Hz, 1H), 7.69 (t, *J* = 53.1 Hz, 1H), 7.40 (dd, *J* = 9.6, 1.5 Hz, 1H), 6.65 (s, 1H), 4.03 (d, *J* = 8.1 Hz, 2H), 3.90 (d, *J* = 8.1 Hz, 2H), 2.95 (t, *J* = 6.3 Hz, 2H), 2.78 (s, 6H), 2.30 (t, *J* = 7.1 Hz, 2H), 1.48 (M, 2H), 1.36 - 1.29 (m, 2H). LC/MS (ESI) (*m/z*): 575 [M+H]⁺.

Example

26:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-(2-azaspiro[3.4]octan-6-yl)imida

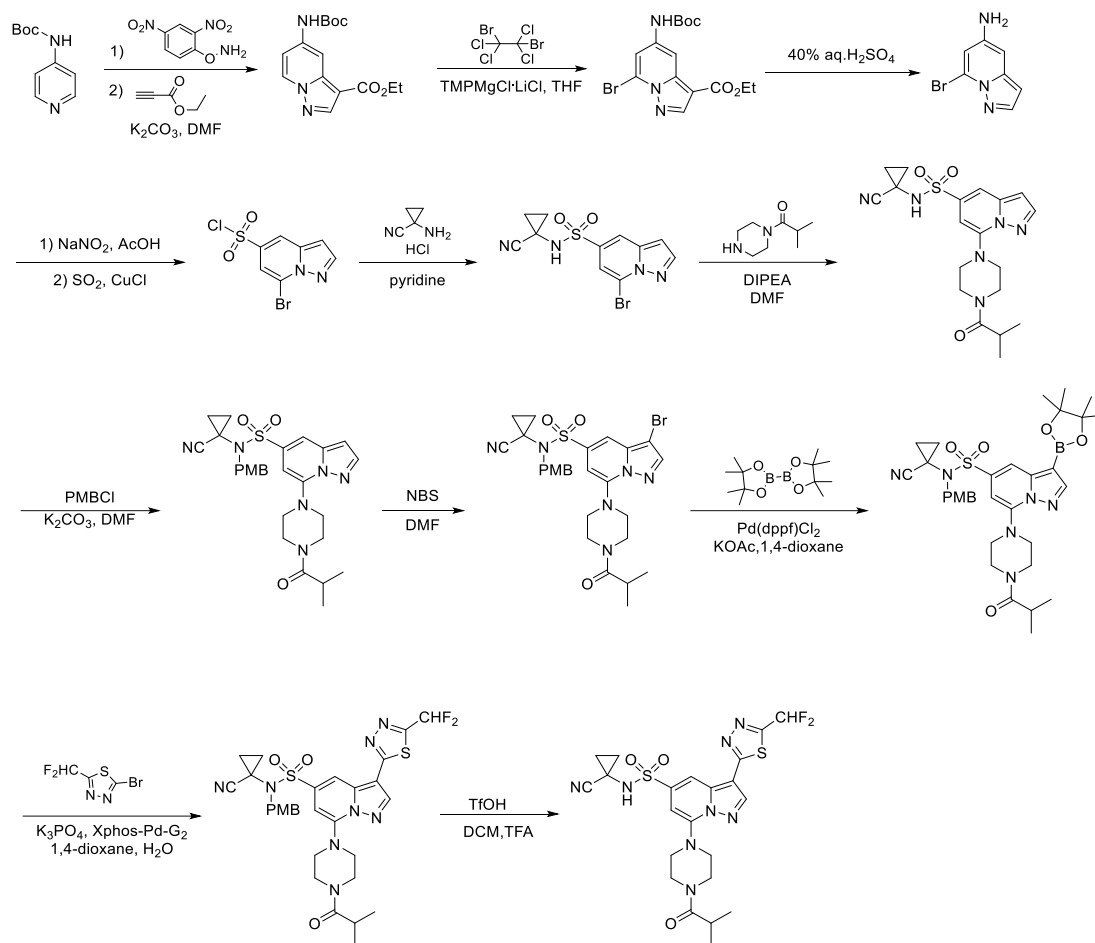
zo[1,5-a]pyridine-6-sulfonamide**Step****1:****Tert-butyl****6-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-1-yl)-2-azaspiro[3.4]octane-2-carboxylate**

At room temperature, Pd/C (5 mg, mass fraction: 10%) was added to the solution of 6-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-1-yl)-2-azaspiro[3.4]octan-6-ene-2-tert-butyl carboxylate (30 mg, 0.05 mmol) in methanol (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred for 5 hours at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (yellow solid, 25 mg, yield: 83.2%). LC/MS (ESI) m/z : 606 $[M+H]^+$.

Step**2:****N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-(2-azaspiro[3.4]octan-6-yl)imidazo[1,5-a]pyridine-6-sulfonamide**

The title compound was prepared by referring to the preparation method in Step 16 of **Example 22** (white solid, 4 mg, yield: 19.2%). ^1H NMR (400 MHz, DMSO- d_6) δ 9.74 (s, 1H), 8.32 (s, 1H), 7.99 (d, J = 9.6 Hz, 1H), 7.79 - 7.53 (m, 1H), 7.28 (d, J = 8.7 Hz, 1H), 3.95 - 3.83 (m, 4H), 3.67 - 3.64 (m, 1H), 2.38 - 2.30 (m, 2H), 2.18 - 2.12 (m, 2H), 2.03 - 1.98 (m, 1H), 1.86 - 1.82 (m, 1H), 1.18 - 1.12 (m, 2H), 1.07 - 1.02 (m, 2H). LC/MS (ESI) (m/z): 506 $[M+H]^+$.

Example**27:****N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-(4-isobutyrylpiperazin-1-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide**



Step 1: Ethyl 5-((tert-butoxycarbonylamino)pyrazolo[1,5-a]pyridine-3-carboxylate

At room temperature, 2,4-dinitrophenylhydrazine (16.4 g, 82.5 mmol) was added portionwise to the solution of 4-(tert-butoxycarbonylamino)pyridine (16 g, 82.5 mmol) in acetonitrile (50 mL); and the reaction mixture was stirred at 40°C for 4 hours. The reaction mixture was concentrated under reduced pressure; the residue was dissolved in N,N-dimethylformamide (160 mL); then, potassium carbonate (22.8 g, 165 mmol) and ethyl propiolate (8.3 mL, 82.5 mmol) were added; and the mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium carbonate solution and saturated brine respectively, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 20-50% ethyl acetate) to obtain the title compound (yellow solid, 8.5 g, yield: 33.9%). LC/MS (ESI) m/z : 306 $[M+H]^+$.

Step 2: Ethyl 7-bromo-5-((tert-butoxycarbonylamino)pyrazolo[1,5-a]pyridine-3-carboxylate

At -78°C, the 2,2,6,6-tetramethylpiperidyl magnesium chloride-lithium chloride complex (57 mL, 57 mmol, 1M in THF) was dropwise added slowly to the solution of 5-((tert-butoxycarbonylamino)pyrazolo[1,5-a]pyridine-3-ethyl carboxylate (7 g, 23.0 mmol) in tetrahydrofuran (90 mL). The reaction mixture was stirred at -78°C for 20 minutes; then,

1,1,2,2-tetrachloro-1,2-dibromoethane (11.2 g, 34.5 mmol) was dropwise added; and thereafter, the reaction mixture was warmed up to room temperature and stirred for 2 hours. The reaction mixture was dropwise added slowly to ice water for quenching, and extracted with ethyl acetate for liquid separation. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 20-50% ethyl acetate) to obtain the title compound (yellow solid, 6.5 g, yield: 73.9%). ¹H NMR (400 MHz, CDCl₃) δ 8.40 (s, 1H), 7.93 (d, *J* = 2.1 Hz, 1H), 7.80 (s, 1H), 6.80 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.55 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H). LC/MS (ESI) *m/z*: 384/386 [M+H]⁺.

Step 3: 7-bromopyrazolo[1,5-a]pyridin-5-amine

7-bromo-5-(tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyridin-3-ethyl carboxylate (3 g, 7.8 mmol) was dissolved in dilute sulphuric acid (40 mL, mass fraction: 40%), and then was stirred at 100°C for 4 hours. The reaction mixture was cooled to room temperature, then adjusted to pH of 7-8 using 4 mol/L aqueous sodium hydroxide solution, and extracted with ethyl acetate three times. The combined organic layers were washed with water and saturated brine, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 1.4 g, yield: 84.7%). LC/MS (ESI) (*m/z*): 212 [M+H]⁺.

Step 4: 7-bromopyrazolo[1,5-a]pyridin-5-sulfonyl chloride

At -10°C, aqueous sodium nitrite solution (322 mg, 4.67 mmol dissolved in 1 mL of water) was dropwise added slowly to the mixed solution of 7-bromopyrazolo[1,5-a]pyridine-5-amine (900 mg, 4.2 mmol) in acetic acid (5 mL) and concentrated hydrochloric acid (5 mL); and the reaction mixture was stirred at -10°C for 45 minutes. In another three-necked flask, cuprous chloride (105 mg, 1.1 mmol) was dissolved in acetic acid (5 mL), and sulfur dioxide was introduced to the resulting mixture for bubbling for 30 minutes at -10°C. The above prepared mixed solution of diazonium salt was dropwise added to the solution of copper chloride and sulfur dioxide in acetic acid; and the reaction mixture was stirred at 10°C for 30 minutes. The reaction mixture was poured into ice water, and extracted with ethyl acetate twice. The combined organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 1.1 g, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) *m/z*: 295 [M+H]⁺.

Step 5: 7-bromo-N-(1-cyanocyclopropyl)pyrazolo[1,5-a]pyridine-5-sulfonamide

At 0°C, 7-bromopyrazolo[1,5-a]pyridin-5-sulfonyl chloride (1.1 g, 4.2 mmol) was added portionwise to the solution of 1-amino-1-cyclopropyl cyanic hydrochloride (500 mg, 4.2 mmol) in pyridine (10 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent:

petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 620 mg, yield: 43.2%). LC/MS (ESI) (m/z): 343 [M+H]⁺.

Step 6: N-(1-cyanocyclopropyl)-7-(4-isobutyrylpiperazin-1-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide

At room temperature, 1-(2-methylacetyl)-piperazine (110 mg, 0.7 mmol) and N,N-diisopropylethylamine (0.3 mL, 1.75 mmol) were sequentially added to the solution of 7-bromo-N-(1-cyanocyclopropyl)pyrazolo[1,5-a]pyridin-5-sulfonamide (200 mg, 0.58 mmol) in N-methylpyrrolidone (3 mL); and the reaction mixture was stirred at 120°C for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (white solid, 220 mg, yield: 90.1%). LC/MS (ESI) (m/z): 417 [M+H]⁺.

Step

7:

N-(1-cyanocyclopropyl)-7-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)pyrazolo[1,5-a]pyridine-5-sulfonamide

At room temperature, potassium carbonate (200 mg, 1.44 mmol) and 4-methoxybenzyl chloride (113 mg, 0.72 mmol) were added to the solution of N-(1-cyanocyclopropyl)-7-[4-isobutyrylpiperazin-1-yl]pyrazolo[1,5-a]pyridin-5-sulfonamide (220 mg, 0.48 mmol) in N,N- (3 mL); and then, the reaction mixture was stirred at 40°C for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 210 mg, yield: 81.5%). LC/MS (ESI) (m/z): 537 [M+H]⁺.

Step

8:

3-bromo-N-(1-cyanocyclopropyl)-7-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)pyrazolo[1,5-a]pyridine-5-sulfonamide

At 0°C, NBS (66 mg, 0.37 mmol) was added portionwise to the solution of N-(1-cyanocyclopropyl)-N-[(4-methoxyphenyl)methyl]-7-[4-(2-methylpropionyl)piperazin-1-yl]pyrazolo[1,5-a]pyridin-5-sulfonamide (200 mg, 0.37 mmol) in N,N- (3 mL); and the reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 200 mg, yield: 87.2%). LC/MS (ESI) (m/z): 617 [M+H]⁺.

Step

9:

N-(1-cyanocyclopropyl)-7-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide

At room temperature, potassium acetate (86 mg, 0.88 mmol) and Pd(dppf)Cl₂ (21 mg, 0.03 mmol) were sequentially added to the solution of 3-bromo-N-(1-cyanocyclopropyl)-7-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)pyrazolo[1,5-a]pyridine-5-sulfonamide (180 mg, 0.29 mmol) and bis(pinacolato)diboron (111 mg, 0.44 mmol) in 1,4-dioxane (3 mL); the flask was replaced with nitrogen gas three times and then the mixture was stirred at 100°C for 5 hours under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 160 mg, yield: 82.6%). LC/MS (ESI) (m/z): 663 [M+H]⁺.

Step

10:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)pyrazolo[1,5-a]pyridine-5-sulfonamide

At room temperature, potassium phosphate (77 mg, 0.36 mmol), XPhos (9.6 mg, 0.02 mmol) and XPhos Pd G2 (10 mg, 0.01 mmol) were sequentially added to the solution of N-(1-cyanocyclopropyl)-7-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaboracyclopentan-2-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide (80 mg, 0.12 mmol) and 2-bromo-5-(difluoromethyl)-1,3,4-thiadiazole (39 mg, 0.18 mmol) in 1,4-dioxane (3 mL) and water (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 100°C for 5 hours under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine twice, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 42 mg, yield: 51.8%). LC/MS (ESI) (m/z): 671 [M+H]⁺.

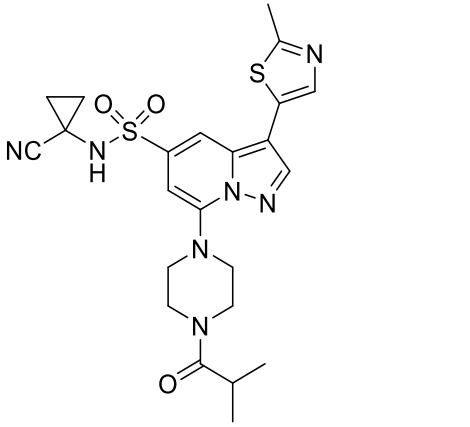
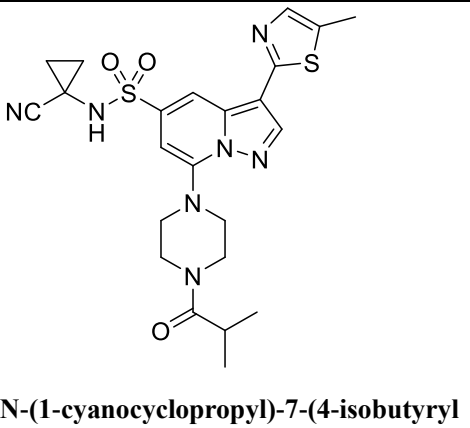
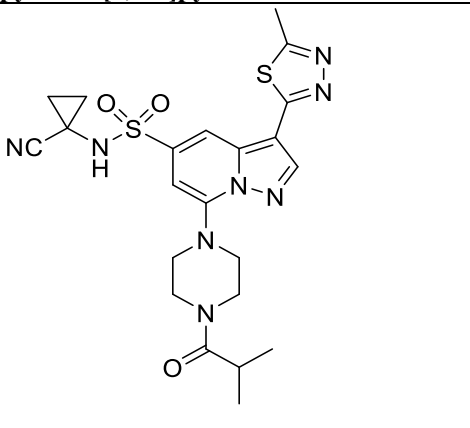
Step

11:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-(4-isobutyrylpiperazin-1-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide

The title compound was prepared by referring to the preparation method in step 9 of **Example 1** (white solid, 9 mg, yield: 49.8%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 8.49 (d, *J* = 1.3 Hz, 1H), 7.67 (t, *J* = 53.3 Hz, 1H), 6.86 (s, 1H), 3.78 (d, *J* = 20.0 Hz, 4H), 3.54 (d, *J* = 24.9 Hz, 4H), 3.00 - 2.93 (m, 1H), 1.47 (t, *J* = 6.7 Hz, 2H), 1.36 (t, *J* = 6.8 Hz, 2H), 1.05 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 551 [M+H]⁺.

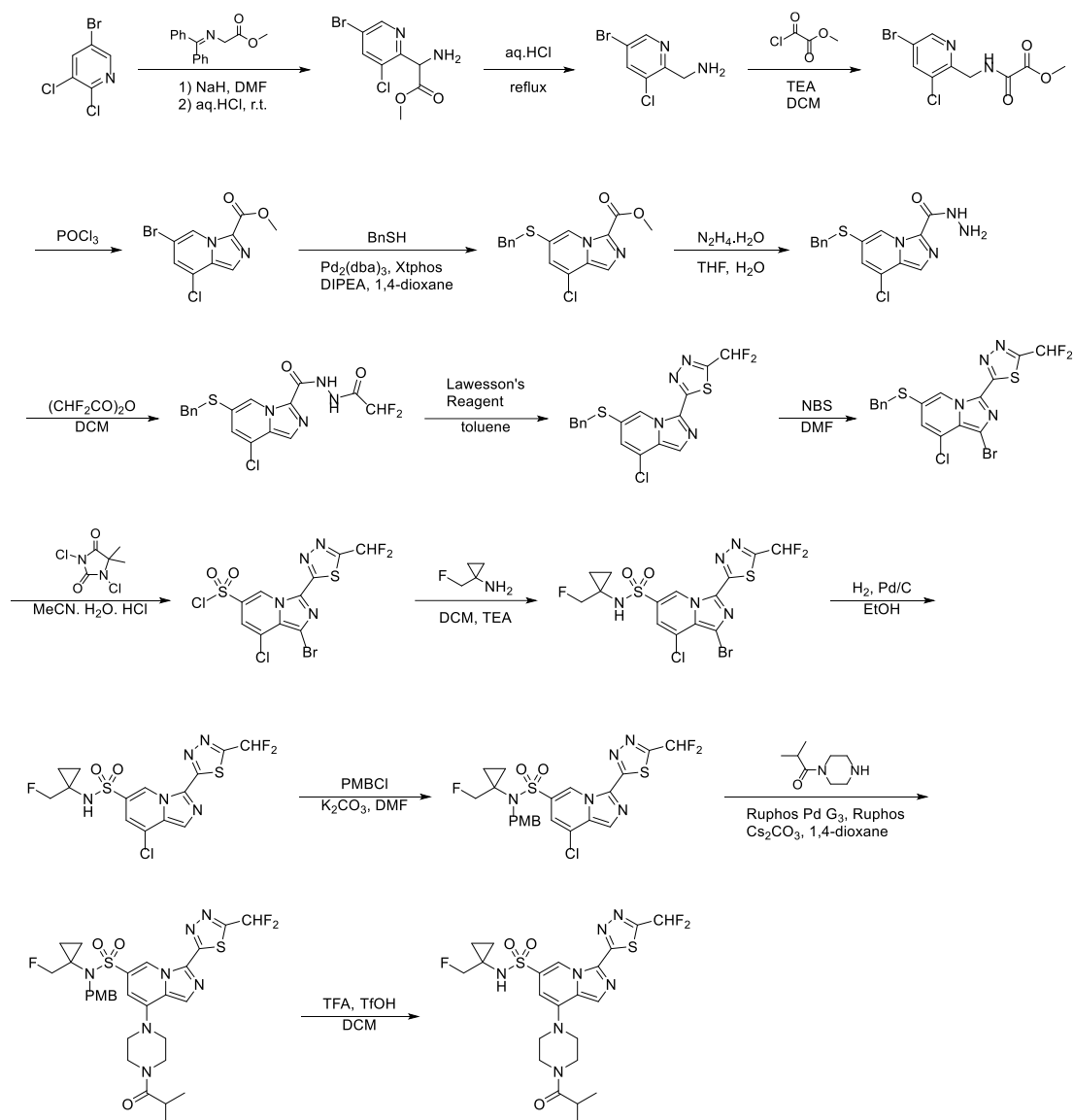
By referring to the preparation method in **Example 27**, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

Example	Structure and name	Analysis data
Example 28	 N-(1-cyanocyclopropyl)-7-(4-isobutyryl piperazin-1-yl)-3-(2-methylthiazol-5-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 7.99 (s, 1H), 7.91 (d, <i>J</i> = 1.4 Hz, 1H), 6.66 (s, 1H), 3.80 - 3.72 (m, 4H), 3.53 - 3.44 (m, 4H), 2.98 - 2.92 (m, 1H), 2.73 (s, 3H), 1.52 - 1.43 (m, 2H), 1.38 - 1.30 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 514 [M+H] ⁺ .
Example 29	 N-(1-cyanocyclopropyl)-7-(4-isobutyryl piperazin-1-yl)-3-(5-methylthiazol-2-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.67 (s, 1H), 8.39 (s, 1H), 7.62 (d, <i>J</i> = 1.2 Hz, 1H), 6.71 (d, <i>J</i> = 1.7 Hz, 1H), 3.80 - 3.72 (m, 4H), 3.52 - 3.46 (m, 4H), 3.43 (s, 3H), 2.99 - 2.95 (m, 1H), 1.34 - 1.29 (m, 2H), 1.25 - 1.23 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 514 [M+H] ⁺ .
Example 30	 N-(1-cyanocyclopropyl)-7-(4-isobutyryl piperazin-1-yl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)pyrazolo[1,5-a]pyridine-5-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.82 (s, 1H), 8.45 (d, <i>J</i> = 1.7 Hz, 1H), 6.80 (d, <i>J</i> = 1.8 Hz, 1H), 3.77 (d, <i>J</i> = 18.8 Hz, 4H), 3.52 (d, <i>J</i> = 23.5 Hz, 4H), 2.98 - 2.94 (m, 1H), 2.80 (s, 3H), 1.47 - 1.44 (m, 2H), 1.38 - 1.34 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 515 [M+H] ⁺ .

Example

31:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Methyl 2-amino-2-(5-bromo-3-chloropyridin-2-yl)acetate

At 0°C, sodium hydride (23.7 g, 592.2 mmol, mass fraction: 60%, dispersed in mineral oil) was added portionwise to 2-[(diphenylmethylene)amino]methyl acetate (50 g, 197.4 mmol) in N,N- (250 mL), during which the temperature was controlled to 0°C, and thereafter, the mixture was continued to be stirred at 0°C for 30 minutes. At 0°C, the solution of 6-bromo-2,3-dichloropyridine (67.2 g, 296.1 mmol) in N,N- (150 mL) was slowly dropwise added to the above mixture; and the mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with 2 mol/L dilute hydrochloric acid at 0°C, and stirred at room temperature for 4 hours. The mixture was neutralized to pH = 8 using 1 mol/L aqueous sodium hydroxide

solution, and extracted with ethyl acetate three times. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude title compound (green solid, 50 g, yield: 90.6%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 279/281 [M+H]⁺.

Step 2: (5-bromo-3-chloropyridin-2-yl)methanamine

2-amino-2-(6-bromo-3-chloropyridin-2-yl)methyl acetate (50 g, 178.9 mmol) was dissolved in 3N dilute hydrochloric acid (700 mL); and then, the resulting mixture was heated to reflux for 3 hours. The reaction mixture was diluted with ethyl acetate, and adjusted to a pH value around 9 by slowly dropwise adding 1 mol/L aqueous sodium hydroxide solution. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the title compound (yellow solid, 13.5g, yield: 34.1%). LC/MS (ESI) (m/z): 221/223 [M+H]⁺.

Step 3: Methyl 2-(((5-bromo-3-chloropyridin-2-yl)methyl)amino)-2-oxoacetate

At 0°C, triethylamine (12 mL, 84.6 mmol) and 2-chloro-2-oxomethyl acetate (5.4 mL, 59.3 mmol) were dropwise added to the solution of (5-bromo-3-chloropyridin-2-yl)methylamine (12.5 g, 56.4 mmol) in tetrahydrofuran (250 mL), after which the mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was added with ice water for quenching, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (brown solid, 12g, yield: 69.1%). LC/MS (ESI) (m/z): 307/309 [M+H]⁺.

Step 4: Methyl 6-bromo-8-chloroimidazo[1,5-a]pyridine-3-carboxylate

At 0°C, 2-(((5-bromo-3-chloropyridin-2-yl)methyl)amino)-2-oxomethyl acetate (12 g, 39.02 mmol) was dissolved in phosphorus oxychloride (80.0 mL); and the reaction mixture was stirred at 110°C for 16 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to remove phosphorus oxychloride; then, ethyl acetate was added; and the resulting mixture was concentrated to take out the residual phosphorus oxychloride. Ice water was added to the residues for quenching; the resulting mixture was extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 5-30% ethyl acetate) to obtain the title compound (brown solid, 5g, yield: 44.3%). LC/MS (ESI) (m/z): 289/291 [M+H]⁺.

Step 5: Methyl 6-(benzylthio)-8-chloroimidazo[1,5-a]pyridine-3-carboxylate

At room temperature and under the nitrogen atmosphere, XantPhos (1.0 g, 1.73 mmol), N,N-diisopropylethylamine (8.6 mL, 51.8 mmol) and Pd₂(dba)₃ (0.79 g, 0.86 mmol) were added to the solution of 6-bromo-8-chloroimidazo[1,5-a]pyridin-3-methyl carboxylate (5 g, 17.3 mmol) and benzyl

mercaptane (3 mL, 25.9 mmol) in 1,4-dioxane (50 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 95°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 10-50% ethyl acetate) to obtain the title compound (white solid, 5 g, yield: 86.9%). LC/MS (ESI) (m/z): 333/335 [M+H]⁺.

Step 6: 6-(benzylthio)-8-chloroimidazo[1,5-a]pyridine-3-carbohydrazide

At room temperature, hydrazine hydrate (1.35 g, 27.0 mmol) was added to the solution of 6-(benzylthioalkyl)-8-chloroimidazo[1,5-a]pyridin-3-methyl formate (1.5 g, 4.5 mmol) in methanol (15 mL); and the mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added; the reaction mixture was extracted with dichloromethane; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 1.4 g, yield: 93.33%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 333/335 [M+H]⁺.

Step 7: 6-(benzylthio)-8-chloro-N'-(2,2-difluoroacetyl)imidazo[1,5-a]pyridine-3-carbohydrazide

At 0°C, difluoroacetic anhydride (1.12 mL, 9.0 mmol) was added to the solution of 6-(benzylthioalkyl)-8-chloroimidazo[1,5-a]pyridin-3-formylhydrazine (1.5 g, 4.5 mmol) in dichloromethane (15 mL); and the mixture was stirred at room temperature for 20 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 1.3 g, yield: 70%). LC/MS (ESI) (m/z): 411/413 [M+H]⁺.

Step 8: 2-(6-(benzylthio)-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

At room temperature, the Lawesson's reagent (1.41 g, 3.48 mmol) was added to the solution of 6-(benzylthio)-8-chloro-N'-(2,2-difluoroacetyl)imidazo[1,5-a]pyridin-3-formylhydrazine (1.3 g, 3.16 mmol) in toluene (15 mL); and the reaction mixture was stirred at 110°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 550 mg, yield: 42.5%). LC/MS (ESI) (m/z): 409/411 [M+H]⁺.

Step

9:

2-(6-(benzylthio)-1-bromo-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

At room temperature, N-bromosuccinimide (105 mg, 0.56 mmol) was added portionwise to the solution of 2-(6-(benzylthio)-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (200 mg, 0.49

mmol) in N,N-dimethylformamide (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, ice water was added for quenching; the reaction mixture was extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow solid, 205 mg, yield: 86%).

Step

10:

1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride

At 0°C, 1,3-dichloro-5,5-dimethylhydantoin (243 mg, 1.23 mmol) was portionwise added to the solution of 2-(6-(benzylthio)-1-bromo-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (200 mg, 0.41 mmol) in acetonitrile (5 mL) and 0.5 N hydrochloric acid (1 mL); and the reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was added with ice water for quenching, and extracted with dichloromethane; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 150 mg, yield: 78.8%), which was directly used in the next reaction..

Step

11:

1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride (200 mg, 0.43 mmol) was added to the solution of 1-(fluoromethyl)cyclopropylamine hydrochloride (108 mg, 0.86 mmol) in pyridine (3 mL); and the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was added with ice water for quenching, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow solid, 110 mg, yield: 49.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.84 (s, 1H), 9.03 (s, 1H), 7.77 (d, *J* = 52.7 Hz, 1H), 7.49 (s, 1H), 4.26 (d, *J* = 48.4 Hz, 2H), 0.93 - 0.89 (m, 2H), 0.83 - 0.79 (m, 2H). LC/MS (ESI) (*m/z*): 517 [M+H]⁺.

Step

12:

8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, Pd/C (15 mg, mass fraction: 10%) was added to the solution of 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)imidazo[1,5-a]pyridin-6-sulfonamide (100 mg, 0.19 mmol) in ethanol (5 mL); the flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 4 hours under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the mixture was filtered. The filtrate was

concentrated under reduced pressure to obtain the title compound (yellow solid, 70 mg, yield: 82.8%). LC/MS (ESI) (m/z): 438 [M+H]⁺.

Step

13:

8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, potassium carbonate (67 mg, 0.48 mmol) and 1-(chloromethyl)-4-methoxybenzene (38 mg, 0.24 mmol) were added to the solution of 8-chloro-3-[5-(difluoromethyl)-1,3,4-thiadiazol-2-yl]-N-[1-(fluoromethyl)cyclopropyl]imidazo[1,5-a]pyridine-6-sulfonamide (80 mg, 0.18 mmol) in N,N- (1 mL); and the reaction mixture was stirred at 40°C for 6 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-15% ethyl acetate) to obtain the title compound (white solid, 80 mg, yield: 89.6%). LC/MS (ESI) (m/z): 558 [M+H]⁺.

Step

14:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, cesium carbonate (137 mg, 0.42 mmol), RuPhos (13 mg, 0.03 mmol) and RuPhos Pd G3 (12 mg, 0.01 mmol) were sequentially added to the solution of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-6-sulfonamide (80 mg, 0.14 mmol) and 1-(2-methylacetyl)-piperazine (34 mg, 0.21 mmol) in 1,4-dioxane (2 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 70°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched, and extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 60 mg, yield: 61.7%). LC/MS (ESI) (m/z): 678 [M+H]⁺.

Step

15:

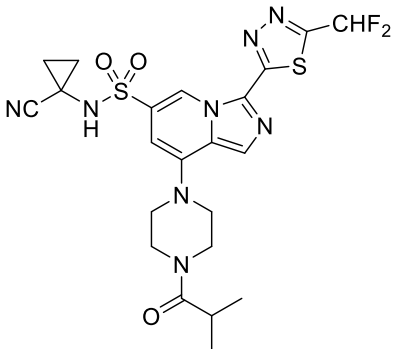
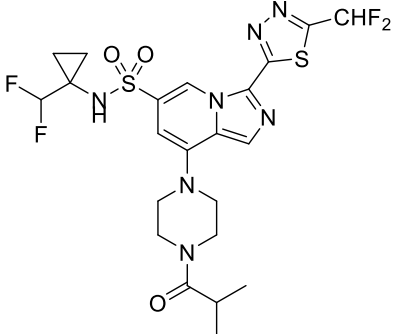
3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

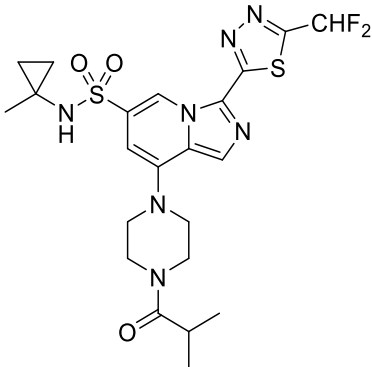
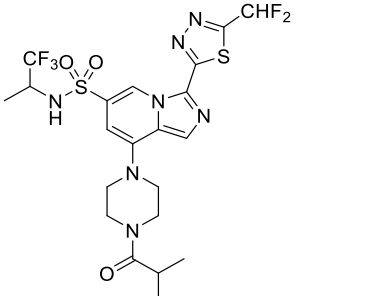
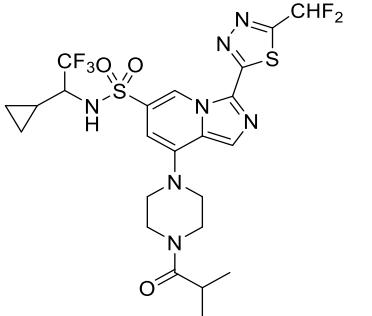
At 0°C, trifluoroacetic acid (0.1 mL) and trifluoromethanesulfonic acid (0.1 mL) were added to the solution of

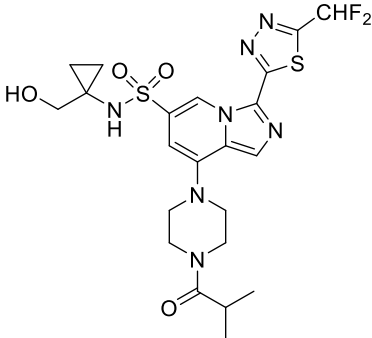
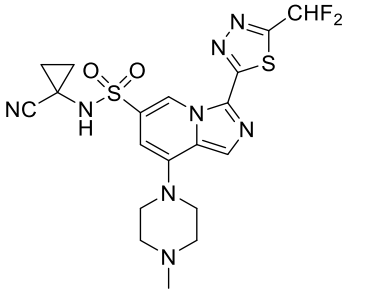
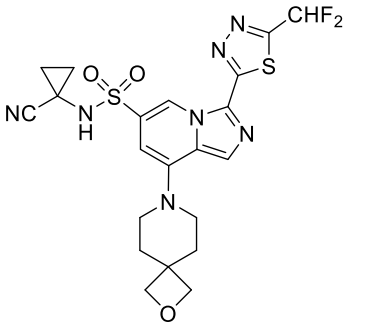
3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-6-sulfonamide (60 mg, 0.09 mmol) in dichloromethane (2 mL);

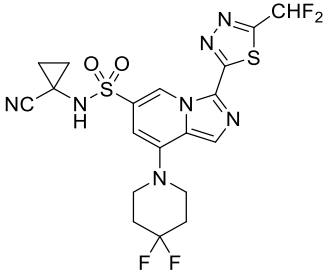
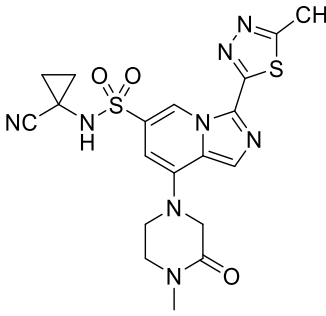
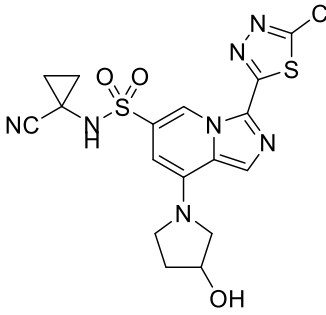
and the reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (white solid, 13 mg, yield: 30.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.58 (s, 1H), 8.82 (s, 1H), 8.07 (s, 1H), 7.68 (t, *J* = 52.8 Hz, 1H), 6.69 (s, 1H), 4.23 (d, *J* = 48.2 Hz, 2H), 3.80 - 3.73 (m, 4H), 3.45 - 3.41 (m, 4H), 2.97 - 2.93 (m, 1H), 1.05 (d, *J* = 5.2 Hz, 6H), 0.89 - 0.84 (m, 2H), 0.81 - 0.76 (m, 2H). LC/MS (ESI) (*m/z*): 558 [M+H]⁺.

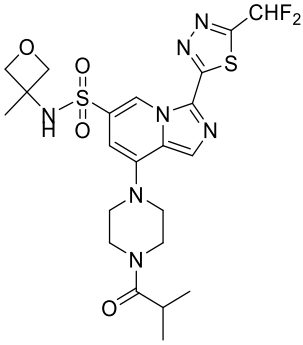
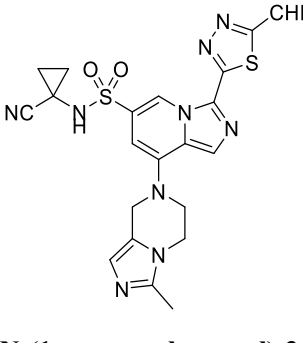
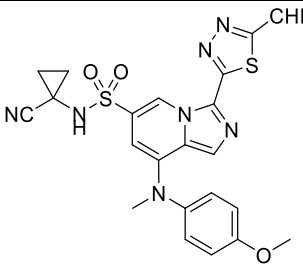
By referring to the preparation method in Example 31, the following examples were implemented according to a similar route by starting from appropriate starting materials.

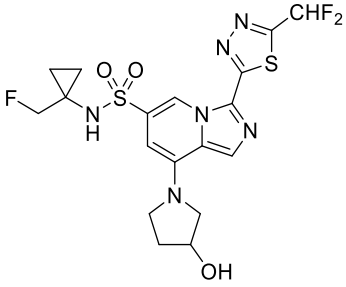
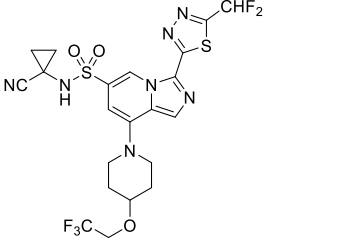
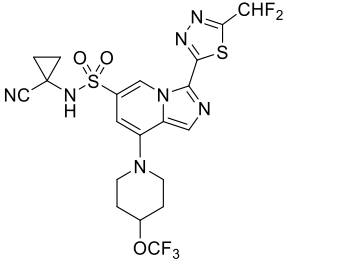
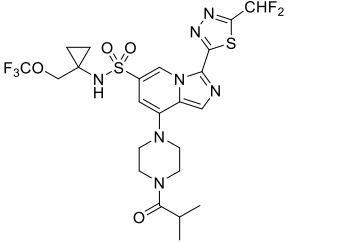
Example	Structure and name	Analysis data
Example 32	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.69 (s, 1H), 9.49 (s, 1H), 8.11 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.68 (s, 1H), 3.88 - 3.68 (m, 4H), 3.32 - 3.27 (m, 4H), 3.03 - 2.87 (m, 1H), 1.56 - 1.46 (m, 2H), 1.42 - 1.35 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 551 [M+H] ⁺ .
Example 33	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(difluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.82 (s, 1H), 7.93 (s, 1H), 7.33 (t, 1H), 6.75 (s, 1H), 5.77 (t, <i>J</i> = 56.9 Hz, 1H), 3.91 - 3.86 (m, 4H), 3.49 - 3.39 (m, 4H), 3.06 - 2.99 (m, 1H), 1.29 - 1.27 (m, 2H), 1.15 (d, <i>J</i> = 6.4 Hz, 6H), 1.04 - 1.02 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 576 [M+H] ⁺ .

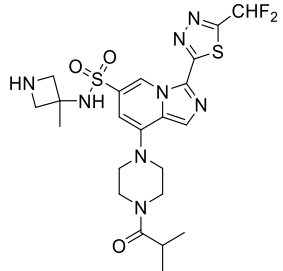
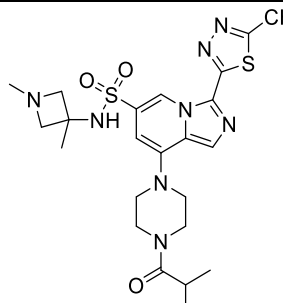
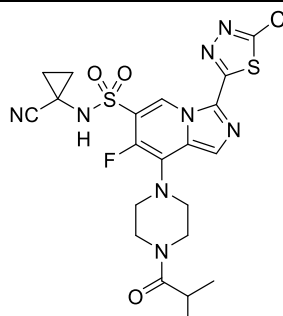
Example 34	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.42 (s, 1H), 8.07 (s, 1H), 7.68 (t, <i>J</i> = 53.4 Hz, 1H), 6.69 (s, 1H), 3.80 - 3.71 (m, 4H), 3.29 - 3.23 (m, 4H), 3.00 - 2.90 (m, 1H), 1.16 (s, 3H), 1.05 (d, <i>J</i> = 6.6 Hz, 6H), 0.75 - 0.70 (m, 2H), 0.48 - 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 540 [M+H]⁺.
Example 35	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1,1,1-trifluoropropan-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.62 (s, 1H), 8.88 (d, <i>J</i> = 8.6 Hz, 1H), 8.08 (s, 1H), 7.62 (d, <i>J</i> = 53.2 Hz, 1H), 6.74 (s, 1H), 4.22 - 4.14 (m, 1H), 3.80 - 3.72 (m, 4H), 3.50 - 3.42 (m, 4H), 2.96 - 2.95 (m, 1H), 1.07 - 1.03 (m, 9H). LC/MS (ESI) (<i>m/z</i>): 582 [M+H]⁺.
Example 36	 N-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.83 (s, 1H), 9.33 (s, 1H), 8.31 (s, 1H), 7.91 (t, <i>J</i> = 53.2 Hz, 1H), 7.04 (s, 1H), 4.04 - 3.96 (m, 4H), 3.80 - 3.68 (m, 4H), 3.50 - 3.47 (m, 1H), 3.20 - 3.15 (m, 1H), 1.28 (d, <i>J</i> = 6.7 Hz, 6H), 1.23 - 1.18 (m, 1H), 0.73 - 0.63 (m, 2H), 0.47 - 0.44 (m, 1H), 0.00 - -0.01 (m, 1H). LC/MS (ESI) (<i>m/z</i>): 608 [M+H]⁺.

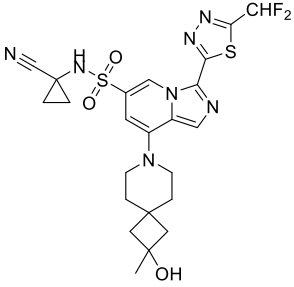
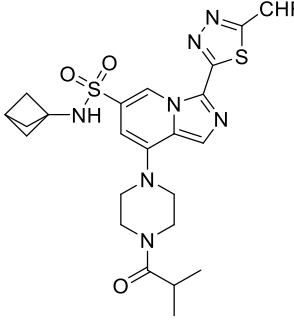
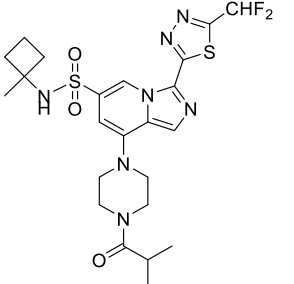
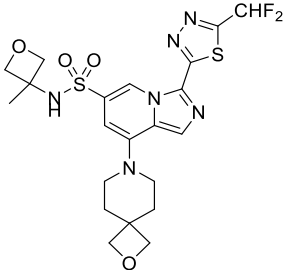
Example 37	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(hydroxymethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.57 (s, 1H), 8.52 (s, 1H), 8.05 (s, 1H), 7.80 - 7.53 (m, 1H), 6.72 (s, 1H), 4.64 (t, <i>J</i> = 5.7 Hz, 1H), 3.75 (d, <i>J</i> = 14.9 Hz, 4H), 3.31 - 3.27 (m, 6H), 2.97 - 2.92 (m, 1H), 1.04 (d, <i>J</i> = 6.7 Hz, 6H), 0.66 - 0.63 (m, 2H), 0.63 - 0.60 (m, 2H). LC/MS (ESI) (m/z): 556 [M+H]⁺.
Example 38	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 8.15 (s, 1H), 8.03 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.66 (s, 1H), 3.32 - 3.30 (m, 4H), 2.62 - 2.58 (m, 4H), 2.30 (s, 3H), 1.50 - 1.46 (m, 2H), 1.40 - 1.36 (m, 2H). LC/MS (ESI) (m/z): 495 [M+H]⁺.
Example 39	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.71 (s, 1H), 9.51 (s, 1H), 8.06 (s, 1H), 7.74 (t, <i>J</i> = 53.2 Hz, 1H), 6.73 (d, <i>J</i> = 0.9 Hz, 1H), 4.47 (s, 4H), 3.35 - 3.31 (m, 4H), 2.13 - 2.08 (m, 4H), 1.56 - 1.51 (m, 2H), 1.47 - 1.42 (m, 2H). LC/MS (ESI) (m/z): 522 [M+H]⁺.

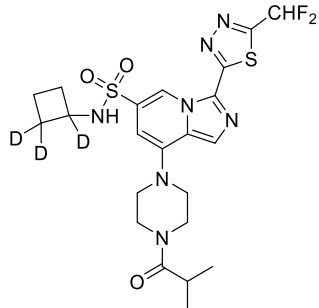
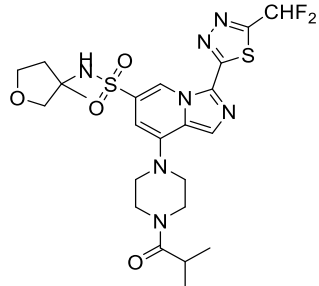
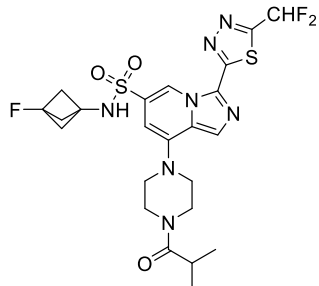
Example 40	 N-(1-cyanocyclopropyl)-3-(5-(difluoroethyl)-1,3,4-thiadiazol-2-yl)-8-(4,4-difluoropiperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 9.48 (s, 1H), 8.10 (s, 1H), 7.82 - 7.55 (m, 1H), 6.74 (s, 1H), 3.50 - 3.45 (m, 4H), 2.31 - 2.21 (m, 4H), 1.51 - 1.45 (m, 2H), 1.43 - 1.38 (m, 2H). LC/MS (ESI) m/z: 516 $[\text{M}+\text{H}]^+$.
Example 41	 N-(1-cyanocyclopropyl)-3-(5-(difluoroethyl)-1,3,4-thiadiazol-2-yl)-8-(4-methyl-3-oxopiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 9.46 (s, 1H), 8.12 (s, 1H), 7.82 - 7.54 (m, 1H), 6.63 (d, $J = 1.0$ Hz, 1H), 3.97 (s, 2H), 3.76 (t, $J = 5.2$ Hz, 2H), 3.57 (t, $J = 5.3$ Hz, 2H), 2.95 (s, 3H), 1.51 - 1.44 (m, 2H), 1.40 - 1.35 (m, 2H). LC/MS (ESI) (m/z): 509 $[\text{M}+\text{H}]^+$.
Example 42	 N-(1-cyanocyclopropyl)-3-(5-(difluoroethyl)-1,3,4-thiadiazol-2-yl)-8-(3-hydroxypyrrolidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 7.81 - 7.54 (m, 1H), 6.11 (s, 1H), 4.52 - 4.44 (m, 1H), 3.90 - 3.75 (m, 3H), 3.71 - 3.67 (m, 1H), 2.12 - 2.05 (m, 1H), 2.04 - 1.97 (m, 1H), 1.35 - 1.29 (m, 2H), 1.26 - 1.21 (m, 2H). LC/MS (ESI) (m/z): 482 $[\text{M}+\text{H}]^+$.

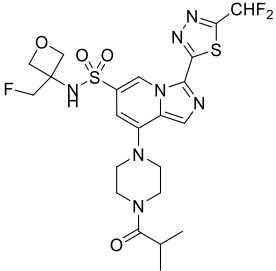
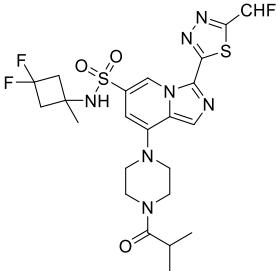
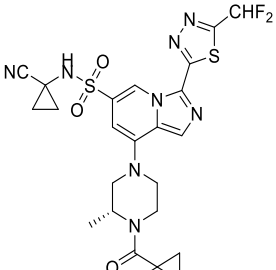
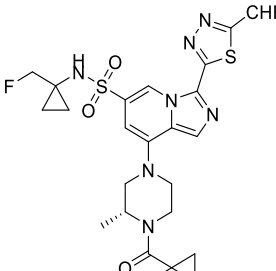
Example 43	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.72 (s, 1H), 8.08 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.70 (s, 1H), 4.63 (d, <i>J</i> = 6.2 Hz, 2H), 4.18 (d, <i>J</i> = 6.3 Hz, 2H), 3.84 - 3.68 (m, 4H), 3.41 - 3.36 (m, 4H), 3.00 - 2.89 (m, 1H), 1.50 (s, 3H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 556 [M+H]⁺.
Example 44	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.70 (s, 1H), 8.13 (d, <i>J</i> = 3.3 Hz, 1H), 7.82 - 7.55 (m, 1H), 6.82 (s, 1H), 6.75 (s, 1H), 4.59 (s, 2H), 4.19 - 4.12 (m, 2H), 3.93 - 3.87 (m, 2H), 2.32 (s, 3H), 1.48 - 1.43 (m, 2H), 1.40 - 1.35 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 532 [M+H]⁺.
Example 45	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4-methoxyphenyl)(methyl)amino)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H), 7.12 - 7.08 (m, 2H), 6.99 - 6.82 (m, 3H), 6.54 (s, 1H), 6.27 (s, 1H), 6.11 (s, 1H), 3.76 (s, 3H), 3.37 (s, 3H), 1.48 - 1.42 (m, 2H), 1.21 - 1.16 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 532 [M+H]⁺.

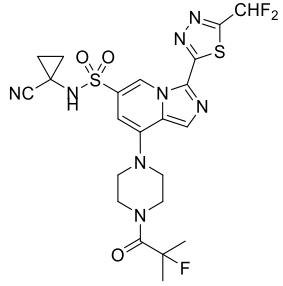
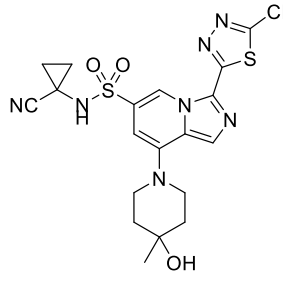
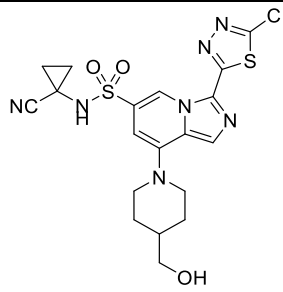
Example 46	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(3-hydroxypyrrolidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.34 (s, 1H), 8.72 (s, 1H), 8.19 (s, 1H), 7.67 (s, 1H), 6.11 (s, 1H), 5.16 - 5.13 (m, 1H), 4.50 - 4.46 (m, 1H), 4.27 (d, <i>J</i> = 48.6 Hz, 2H), 3.86 - 3.75 (m, 2H), 3.72 - 3.66 (m, 1H), 0.87 - 0.81 (m, 4H), 0.78 - 0.75 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 489 [M+H]⁺.
Example 47	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(2,2,2-trifluoroethoxy)piperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.47 (s, 1H), 8.03 (s, 1H), 7.68 (t, 1H), 6.68 (s, 1H), 4.19 - 4.13 (m, 2H), 3.84 - 3.79 (m, 1H), 3.61 - 3.57 (m, 2H), 3.19 - 3.14 (m, 2H), 2.12 - 2.04 (m, 2H), 1.82 - 1.75 (m, 2H), 1.50 - 1.47 (m, 2H), 1.41 - 1.37 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 578 [M+H]⁺.
Example 48	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(trifluoromethoxy)piperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.48 (s, 1H), 8.05 (s, 1H), 7.82 - 7.54 (m, 1H), 6.69 (s, 1H), 4.80 - 4.71 (m, 1H), 3.63 - 3.56 (m, 2H), 3.26 (d, <i>J</i> = 9.4 Hz, 2H), 2.21 - 2.13 (m, 2H), 2.01 - 1.93 (m, 2H), 1.51 - 1.45 (m, 2H), 1.41 - 1.35 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 564 [M+H]⁺.
Example 49	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-(2,2,2-trifluoroethoxy)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.88 (s, 1H), 8.07 (s, 1H), 7.82 - 7.54 (m, 1H), 6.68 (s, 1H), 3.95 (s, 2H), 3.80 - 3.71 (m, 4H), 3.29 - 3.24 (m, 4H), 2.99 - 2.91 (m, 1H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H), 0.91 - 0.87 (m, 2H), 0.85 - 0.80 (m, 2H). LC/MS (ESI)

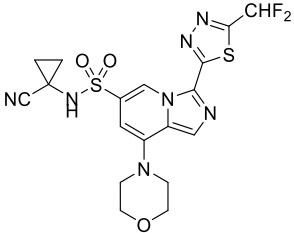
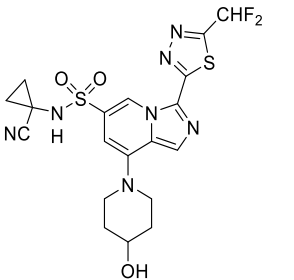
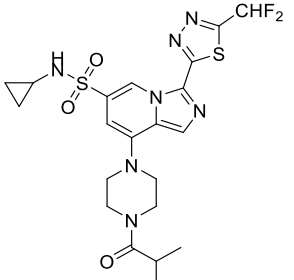
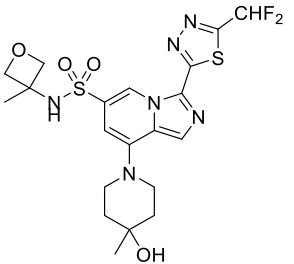
	(trifluoromethoxy)methyl)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	(m/z): 624 [M+H] ⁺ .
Example 50	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methylazetidin-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 8.27 (s, 1H), 8.07 (s, 1H), 7.81 - 7.54 (m, 1H), 6.72 (s, 1H), 3.80 - 3.73 (m, 6H), 3.33 - 3.23 (m, 6H), 2.98 - 2.92 (m, 1H), 1.46 (s, 3H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 555 [M+H] ⁺ .
Example 51	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1,3-dimethylazetidin-3-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 8.15 (s, 1H), 8.07 (s, 1H), 7.81 - 7.54 (m, 1H), 6.73 (s, 1H), 3.84 - 3.68 (m, 5H), 3.15 - 3.08 (m, 5H), 2.97 - 2.92 (m, 1H), 2.19 (d, <i>J</i> = 3.7 Hz, 3H), 1.41 (s, 3H), 1.05 (d, <i>J</i> = 6.6 Hz, 6H). LC/MS (ESI) (m/z): 569 [M+H] ⁺ .
Example 52	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.72 (d, <i>J</i> = 5.1 Hz, 1H), 8.01 (s, 1H), 7.67 (t, 1H), 3.74 - 3.66 (m, 4H), 3.47 - 3.43 (m, 4H), 2.97 - 2.91 (m, 1H), 1.55 - 1.47 (m, 2H), 1.44 - 1.37 (m, 2H), 1.04 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 569 [M+H] ⁺ .

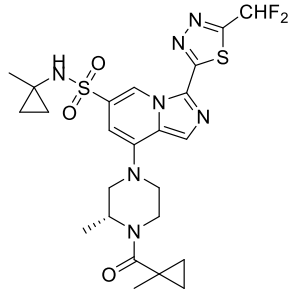
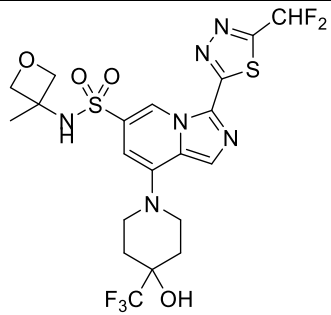
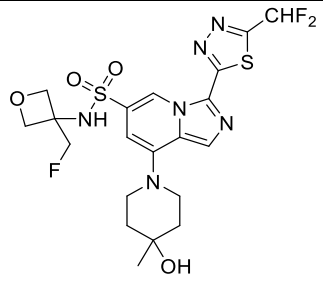
Example 53	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-hydroxy-2-methyl-7-azaspiro[3.5]nonan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 9.44 (s, 1H), 7.97 (s, 1H), 7.61 (d, <i>J</i> = 53.0 Hz, 1H), 6.65 (s, 1H), 4.83 (s, 1H), 3.25 (s, 4H), 1.92 (d, <i>J</i> = 2.9 Hz, 4H), 1.85 (s, 2H), 1.75 (s, 2H), 1.47 (d, <i>J</i> = 4.1 Hz, 2H), 1.39 (d, <i>J</i> = 4.3 Hz, 2H), 1.29 (s, 3H). LC/MS (ESI) (m/z): 550 [M+H]⁺.
Example 54	 N-(bicyclo[1.1.1]pentan-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.84 (s, 1H), 7.94 (s, 1H), 7.49 - 7.17 (m, 1H), 6.75 (d, <i>J</i> = 1.0 Hz, 1H), 3.89 (d, <i>J</i> = 3.7 Hz, 4H), 3.41 (s, 2H), 3.35 (s, 2H), 3.08 - 2.99 (m, 1H), 2.31 (s, 1H), 1.92 (s, 6H), 1.16 (s, 3H), 1.14 (s, 3H). LC/MS (ESI) (m/z): 552 [M+H]⁺.
Example 55	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclobutyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.21 (s, 1H), 8.07 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.76 (s, 1H), 3.85 - 3.69 (m, 4H), 3.33 - 3.26 (m, 4H), 3.01 - 2.91 (m, 1H), 2.27 - 2.15 (m, 2H), 1.77 - 1.69 (m, 2H), 1.68 - 1.58 (m, 2H), 1.35 (s, 3H), 1.06 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 553 [M+H]⁺.
Example 56		¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.56 (s, 1H), 8.70 (s, 1H), 7.97 (s, 1H), 7.67 (t, <i>J</i> = 53.2 Hz, 1H), 6.69 (s, 1H), 4.62 (d, <i>J</i> = 6.1 Hz, 2H), 4.41 (s, 4H), 4.18 (d, <i>J</i> = 6.3 Hz, 2H), 3.27 - 3.23 (m,

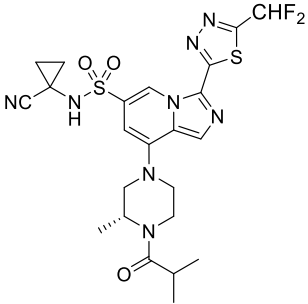
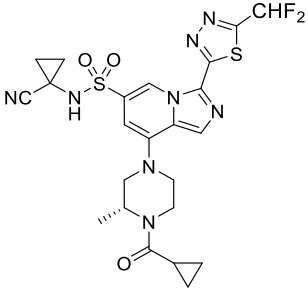
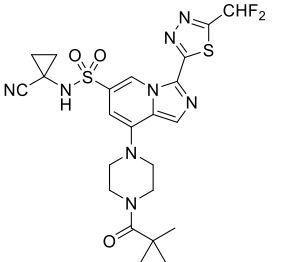
	3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide	4H), 2.07 - 2.00 (m, 4H), 1.49 (s, 3H). LC/MS (ESI) (m/z): 527 [M+H] ⁺ .
Example 57	 N-(cyclobutyl-1,2,2-d₃)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.57 (s, 1H), 8.34 (s, 1H), 8.06 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.70 (s, 1H), 3.80 - 3.73 (m, 4H), 3.32 - 3.24 (m, 4H), 2.99 - 2.93 (m, 1H), 1.99 - 1.94 (m, 1H), 1.84 - 1.77 (m, 1H), 1.50 - 1.43 (m, 2H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 543 [M+H] ⁺ .
Example 58	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyltetrahydrofuran-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.61 (s, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 7.67 (t, <i>J</i> = 53.2 Hz, 1H), 6.78 (s, 1H), 3.82 - 3.68 (m, 8H), 3.32 - 3.26 (m, 4H), 2.98 - 2.92 (m, 1H), 2.22 - 2.15 (m, 1H), 1.81 - 1.73 (m, 1H), 1.27 (s, 3H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 570 [M+H] ⁺ .
Example 59	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-fluorobicyclo[1.1.1]pentan-1-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 9.89 (s, 1H), 7.74 (s, 1H), 7.21 - 6.96 (m, 1H), 6.65 (s, 1H), 5.74 (s, 1H), 3.96 - 3.78 (m, 4H), 3.42 - 3.30 (m, 4H), 2.91 - 2.82 (m, 1H), 2.39 - 2.32 (m, 6H), 1.22 - 1.17 (m, 6H). LC/MS (ESI) (m/z): 570 [M+H] ⁺ .

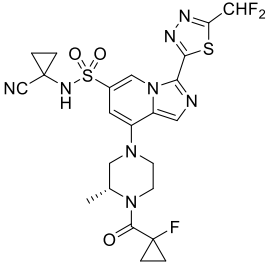
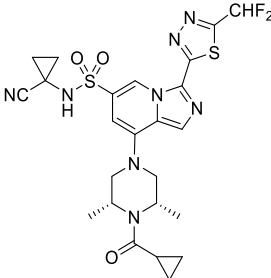
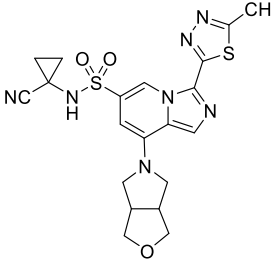
Example 60	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.85 (s, 1H), 7.94 (s, 1H), 7.46 - 7.20 (m, 2H), 6.79 (s, 1H), 4.81 - 4.78 (m, 4H), 4.48 (d, <i>J</i> = 7.0 Hz, 2H), 3.49 - 3.40 (m, 4H), 3.38 - 3.34 (m, 4H), 3.06 - 2.99 (m, 1H), 1.15 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 574 [M+H]⁺.
Example 61	 N-(3,3-difluoro-1-methylcyclobutyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.64 (s, 1H), 8.07 (s, 1H), 7.61 (d, <i>J</i> = 53.0 Hz, 1H), 6.71 (s, 1H), 3.76 (d, <i>J</i> = 14.6 Hz, 4H), 3.37 - 3.32 (m, 4H), 2.95 - 2.92 (m, 1H), 2.88 - 2.84 (m, 2H), 2.60 - 2.54 (m, 2H), 1.36 (s, 3H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H).LC/MS (ESI) (m/z): 590 [M+H]⁺.
Example 62	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carboxyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.68 (s, 1H), 9.47 (s, 1H), 7.99 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.68 (s, 1H), 4.68 (d, <i>J</i> = 6.1 Hz, 1H), 4.27 (d, <i>J</i> = 13.4 Hz, 1H), 3.76 - 3.65 (m, 2H), 3.64 - 3.35 (m, 1H), 3.08 - 3.01 (m, 1H), 3.00 - 2.86 (m, 1H), 1.51 - 1.45 (m, 2H), 1.43 - 1.34 (m, 5H), 1.28 (s, 3H), 0.90 - 0.80 (m, 2H), 0.62 - 0.53 (m, 2H). LC/MS (ESI) (m/z): 577 [M+H]⁺.
Example 63		¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), 8.82 (s, 1H), 7.96 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.71 (s, 1H), 4.74 - 4.60 (m, 1H), 4.35 - 4.24 (m, 2H), 4.22 - 4.13 (m, 1H), 3.73 - 3.62 (m,

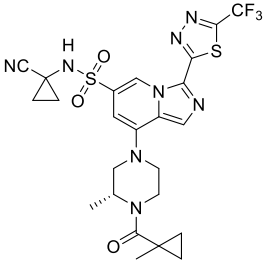
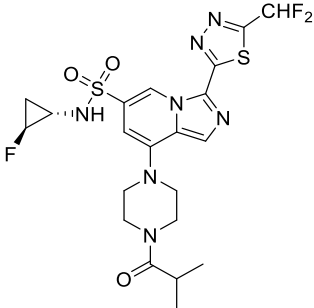
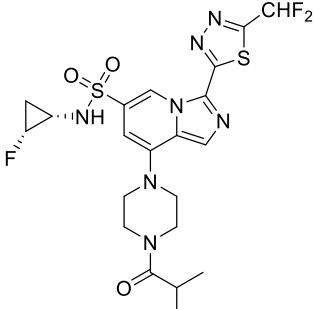
	(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	2H), 3.05 - 2.97 (m, 1H), 2.95 - 2.82 (m, 1H), 1.40 - 1.38 (m, 2H), 1.28 (s, 3H), 1.26 - 1.24 (m, 2H), 0.91 - 0.81 (m, 4H), 0.80 - 0.76 (m, 2H), 0.63 - 0.55 (m, 2H). LC/MS (ESI) (m/z): 584 [M+H]⁺.
Example 64	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(2-fluoro-2-methylpropanoyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.69 (s, 1H), 9.47 (s, 1H), 8.11 (s, 1H), 7.69 (t, <i>J</i> = 53.1 Hz, 1H), 6.69 (s, 1H), 4.01 - 3.75 (m, 4H), 3.41 - 3.37 (m, 4H), 1.63 (s, 3H), 1.57 (s, 3H), 1.50 - 1.46 (m, 2H), 1.41 - 1.36 (m, 2H). LC/MS (ESI) (m/z): 568 [M+H]⁺.
Example 65	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxy-4-methylpiperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.63 (s, 1H), 9.45 (s, 1H), 7.99 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.67 (d, <i>J</i> = 1.0 Hz, 1H), 4.44 (s, 1H), 3.50 - 3.44 (m, 2H), 3.30 - 3.26 (m, 2H), 1.78 - 1.72 (m, 2H), 1.69 - 1.64 (m, 2H), 1.49 - 1.45 (m, 2H), 1.40 - 1.37 (m, 2H), 1.22 (s, 3H). LC/MS (ESI) (m/z): 510 [M+H]⁺.
Example 66	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxymethylpiperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 9.47 (s, 1H), 7.98 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.66 (d, <i>J</i> = 0.9 Hz, 1H), 4.57 (t, <i>J</i> = 5.2 Hz, 1H), 3.81 (d, <i>J</i> = 12.5 Hz, 2H), 3.40 (s, 2H), 2.92 (t, <i>J</i> = 10.6 Hz, 2H), 1.86 (d, <i>J</i> = 11.2 Hz, 2H), 1.66 (s, 1H), 1.50 - 1.38 (m, 6H). LC/MS (ESI) (m/z): 510 [M+H]⁺.

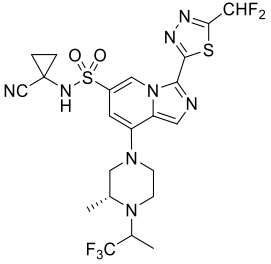
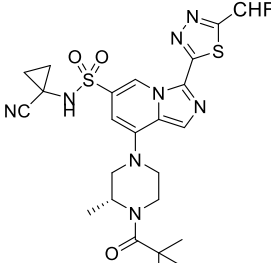
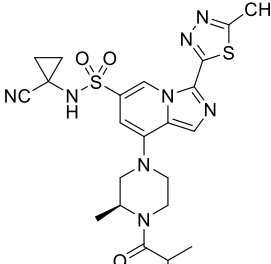
Example 67	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-morpholinoimidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.69 (s, 1H), 9.49 (s, 1H), 8.09 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.68 (s, 1H), 3.89 - 3.84 (m, 4H), 3.31 - 3.29 (m, 4H), 1.48 (t, <i>J</i> = 6.8 Hz, 2H), 1.38 (t, <i>J</i> = 6.9 Hz, 2H). LC/MS (ESI) (<i>m/z</i>): 482 [M+H]⁺.
Example 68	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxypiperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 9.46 (s, 1H), 7.99 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.66 (d, <i>J</i> = 1.2 Hz, 1H), 4.81 (d, <i>J</i> = 4.0 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.65 - 3.58 (m, 2H), 3.14 - 3.07 (m, 2H), 1.97 - 1.90 (m, 2H), 1.68 - 1.59 (m, 2H), 1.49 - 1.44 (m, 2H), 1.40 - 1.34 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 496 [M+H]⁺.
Example 69	 N-cyclopropyl-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.62 (s, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.70 (s, 1H), 3.82 - 3.72 (m, 4H), 3.37 - 3.35 (m, 4H), 2.97 - 2.93 (m, 1H), 2.28 - 2.23 (m, 1H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H), 0.54 - 0.50 (m, 2H), 0.49 - 0.46 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 526 [M+H]⁺.
Example 70	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxy-4-methylpiperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.54 (s, 1H), 8.70 (s, 1H), 7.96 (s, 1H), 7.67 (t, <i>J</i> = 53.2 Hz, 1H), 6.71 (s, 1H), 4.62 (d, <i>J</i> = 6.1 Hz, 2H), 4.46 (s, 1H), 4.18 (d, <i>J</i> = 6.3 Hz, 2H), 3.48 - 3.43 (m, 2H), 3.28 - 3.24 (m, 2H), 1.79 - 1.65 (m, 4H), 1.49 (s, 3H), 1.23 (s, 3H).

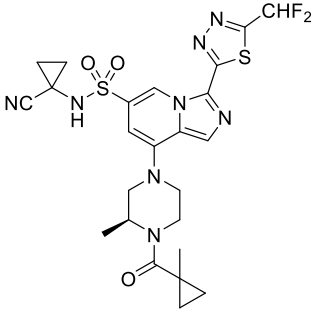
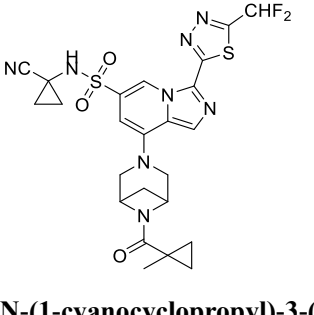
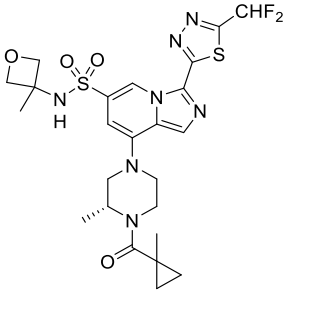
	)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	LC/MS (ESI) (m/z): 515 [M+H] ⁺ .
Example 71	 (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.61 (s, 1H), 8.44 (s, 1H), 7.97 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.71 (s, 1H), 4.69 (dd, <i>J</i> = 6.9, 5.0 Hz, 1H), 4.33 - 4.22 (m, 1H), 3.74 - 3.61 (m, 2H), 3.47 - 3.40 (m, 1H), 3.08 - 2.99 (m, 1H), 2.97 - 2.86 (m, 1H), 1.44 - 1.36 (m, 3H), 1.28 (s, 3H), 1.17 (s, 3H), 0.90 - 0.82 (m, 2H), 0.77 - 0.68 (m, 2H), 0.62 - 0.57 (m, 2H), 0.49 - 0.44 (m, 2H). LC/MS (ESI) (m/z): 566 [M+H] ⁺ .
Example 72	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxy-4-(trifluoromethyl)piperidin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.58 (s, 1H), 8.73 (s, 1H), 8.06 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.76 (s, 1H), 6.15 (s, 1H), 4.63 (d, <i>J</i> = 6.2 Hz, 2H), 4.19 (d, <i>J</i> = 6.3 Hz, 2H), 3.72 - 3.66 (m, 2H), 3.16 - 3.11 (m, 2H), 2.07 - 1.99 (m, 2H), 1.89 - 1.83 (m, 2H), 1.49 (s, 3H). LC/MS (ESI) m/z: 569 [M+H] ⁺ .
Example 73	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-hydroxy-4-methylpiperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.55 (s, 1H), 9.04 (s, 1H), 7.96 (s, 1H), 7.67 (t, <i>J</i> = 53.2 Hz, 1H), 6.73 (s, 1H), 4.72 (s, 1H), 4.65 - 4.62 (m, 2H), 4.60 (s, 1H), 4.45 (s, 1H), 4.38 (d, <i>J</i> = 6.9 Hz, 2H), 3.48 - 3.43 (m, 2H), 3.30 - 3.22 (m, 2H), 1.80 - 1.72 (m, 2H), 1.70 - 1.64 (m, 2H), 1.22 (s, 3H). LC/MS (ESI) (m/z): 533 [M+H] ⁺ .

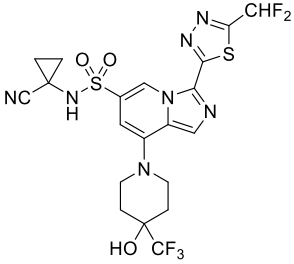
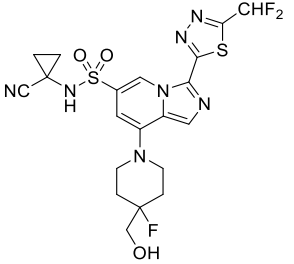
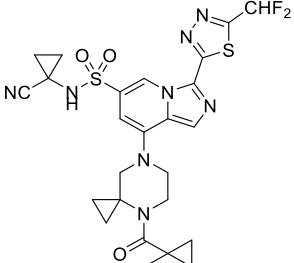
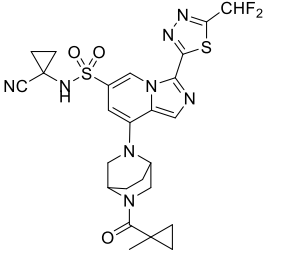
Example 74	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 9.48 (s, 1H), 8.00 (s, 1H), 7.69 (t, J = 53.2 Hz, 1H), 6.66 (s, 1H), 4.77 - 4.38 (m, 1H), 3.74 - 3.66 (m, 2H), 3.37 - 3.34 (m, 2H), 3.16 - 2.99 (m, 2H), 2.94 - 2.89 (m, 1H), 1.50 - 1.47 (m, 2H), 1.40 - 1.37 (m, 2H), 1.33 - 1.22 (m, 3H), 1.05 (d, J = 6.6 Hz, 6H). LC/MS (ESI) (m/z): 565 $[\text{M}+\text{H}]^+$.
Example 75	 (R)-N-(1-cyanocyclopropyl)-8-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.49 (s, 1H), 8.02 (s, 1H), 7.69 (t, J = 53.1 Hz, 1H), 6.67 (s, 1H), 4.76 - 4.66 (m, 1H), 4.30 - 4.27 (m, 1H), 3.77 - 3.74 (m, 3H), 3.07 - 2.87 (m, 2H), 1.49 - 1.39 (m, 8H), 0.86 - 0.78 (m, 4H). LC/MS (ESI) (m/z): 563 $[\text{M}+\text{H}]^+$.
Example 76	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 9.47 (s, 1H), 8.11 (s, 1H), 7.82 - 7.53 (m, 1H), 6.70 (s, 1H), 3.82 (s, 4H), 3.42 - 3.39 (m, 2H), 3.32 - 3.28 (m, 2H), 1.53 - 1.47 (m, 2H), 1.42 - 1.37 (m, 2H), 1.29 (s, 3H), 0.88 - 0.85 (m, 2H), 0.61 - 0.57 (m, 2H). LC/MS (ESI) m/z: 563 $[\text{M}+\text{H}]^+$.

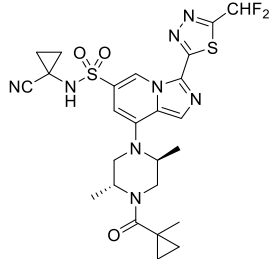
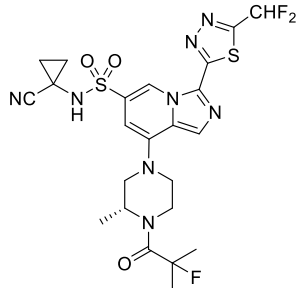
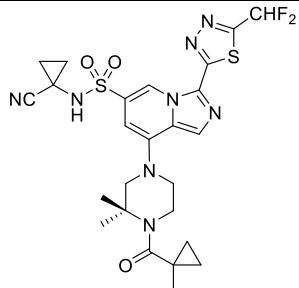
Example 77	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-fluorocyclopropane-1-carbonyl)-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.69 (s, 1H), 9.47 (s, 1H), 8.02 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.69 (s, 1H), 4.72 - 4.61 (m, 1H), 4.33 - 4.18 (m, 1H), 3.84 - 3.71 (m, 2H), 3.50 - 3.41 (m, 1H), 3.18 - 3.12 (m, 1H), 3.04 - 2.93 (m, 1H), 1.53 - 1.42 (m, 5H), 1.41 - 1.37 (m, 2H), 1.35 - 1.32 (m, 1H), 1.30 - 1.20 (m, 3H). LC/MS (ESI) <i>m/z</i>: 581 [M+H]⁺.
Example 78	 N-(1-cyanocyclopropyl)-8-((3R,5S)-4-(cyclopropanecarbonyl)-3,5-dimethylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.71 (s, 1H), 9.52 (s, 1H), 7.91 (s, 1H), 7.70 (t, <i>J</i> = 53.1 Hz, 1H), 6.75 (s, 1H), 4.66 (s, 2H), 3.68 (d, <i>J</i> = 11.9 Hz, 2H), 3.16 - 2.96 (m, 2H), 2.06 - 1.94 (m, 1H), 1.56 - 1.32 (m, 10H), 0.85 - 0.73 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 577 [M+H]⁺.
Example 79	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.49 (s, 1H), 9.40 (s, 1H), 8.24 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.18 (s, 1H), 3.96 - 3.82 (m, 4H), 3.72 (d, <i>J</i> = 8.9 Hz, 2H), 3.60 (d, <i>J</i> = 9.4 Hz, 2H), 3.15 (s, 2H), 1.51 - 1.44 (m, 2H), 1.40 - 1.32 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 508 [M+H]⁺.

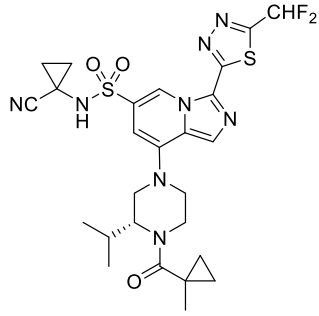
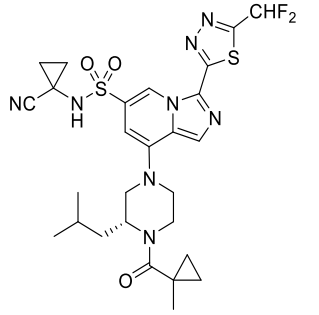
Example 80	 (R)-N-(1-cyanocyclopropyl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.51 (s, 1H), 8.04 (s, 1H), 6.72 (s, 1H), 4.69 (s, 1H), 4.27 (d, <i>J</i> = 13.1 Hz, 1H), 3.71 (dd, <i>J</i> = 26.3, 11.2 Hz, 2H), 3.57 - 3.45 (m, 1H), 3.05 (d, <i>J</i> = 10.4 Hz, 1H), 2.99 - 2.89 (m, 1H), 1.49 (s, 2H), 1.39 (s, 5H), 1.28 (s, 3H), 0.90 - 0.81 (m, 2H), 0.61 - 0.55 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 595 [M+H]⁺.
Example 81	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((1S,2S)-2-fluorocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.63 (s, 1H), 8.45 (s, 1H), 8.09 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.67 (s, 1H), 4.70 (d, <i>J</i> = 60.3 Hz, 1H), 3.80 - 3.73 (m, 4H), 3.42 - 3.36 (m, 4H), 2.98 - 2.92 (m, 1H), 2.74 - 2.67 (m, 1H), 1.30 - 1.19 (m, 1H), 1.05 (d, <i>J</i> = 6.5 Hz, 6H), 1.03 - 0.90 (m, 1H). LC/MS (ESI) (<i>m/z</i>): 544 [M+H]⁺.
Example 82	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((1S,2R)-2-fluorocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.63 (s, 1H), 8.51 (s, 1H), 8.08 (s, 1H), 7.69 (t, <i>J</i> = 53.1 Hz, 1H), 6.74 (s, 1H), 4.70 - 4.49 (m, 1H), 3.76 (d, <i>J</i> = 16.0 Hz, 4H), 3.32 - 3.27 (m, 4H), 2.99 - 2.91 (m, 1H), 2.36 - 2.30 (m, 1H), 1.26 - 1.22 (m, 1H), 1.05 (d, <i>J</i> = 6.5 Hz, 6H), 0.99 - 0.92 (m, 1H). LC/MS (ESI) (<i>m/z</i>): 544 [M+H]⁺.

Example 83	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R)-3-methyl-4-(1,1,1-trifluoropropan-2-yl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.46 (s, 1H), 8.04 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.65 (s, 1H), 3.89 - 3.80 (m, 1H), 3.78 - 3.72 (m, 1H), 3.65 - 3.59 (m, 1H), 2.98 - 2.90 (m, 3H), 2.85 - 2.78 (m, 1H), 2.75 - 2.67 (m, 1H), 1.51 - 1.45 (m, 2H), 1.42 - 1.36 (m, 2H), 1.22 - 1.18 (m, 3H), 1.16 - 1.12 (m, 3H). LC/MS (ESI) (<i>m/z</i>): 591 [M+H]⁺.
Example 84	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-pivaloylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.68 (s, 1H), 9.48 (s, 1H), 7.98 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.67 (s, 1H), 4.72 (s, 1H), 4.27 (d, <i>J</i> = 12.7 Hz, 1H), 3.74 - 3.64 (m, 2H), 3.48 (s, 1H), 3.04 (d, <i>J</i> = 11.2 Hz, 1H), 2.95 - 2.85 (m, 1H), 1.53 - 1.49 (m, 2H), 1.46 - 1.39 (m, 5H), 1.25 (s, 9H). LC/MS (ESI) (<i>m/z</i>): 579 [M+H]⁺.
Example 85	 (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 9.53 (s, 1H), 7.99 (s, 1H), 7.68 (t, <i>J</i> = 53.3 Hz, 1H), 6.66 (s, 1H), 4.77 - 4.37 (m, 1H), 4.00 - 3.61 (m, 3H), 3.25 - 2.70 (m, 4H), 1.49 - 1.47 (m, 3H), 1.41 - 1.25 (m, 4H), 1.05 (d, <i>J</i> = 6.4 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 565 [M+H]⁺.

Example 86	 (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.47 (s, 1H), 7.99 (s, 1H), 7.68 (t, J = 53.0 Hz, 1H), 6.68 (s, 1H), 4.77 - 4.62 (m, 1H), 4.34 - 4.19 (m, 1H), 3.79 - 3.63 (m, 2H), 3.61 - 3.36 (m, 1H), 3.07 - 3.00 (m, 1H), 2.98 - 2.87 (m, 1H), 1.53 - 1.46 (m, 2H), 1.43 - 1.34 (m, 5H), 1.28 (s, 3H), 0.90 - 0.79 (m, 2H), 0.62 - 0.55 (m, 2H). LC/MS (ESI) (m/z): 577 $[\text{M}+\text{H}]^+$.
Example 87	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(6-(1-methylcyclopropane-1-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 9.40 (s, 1H), 8.38 (s, 1H), 7.68 (t, J = 53.3 Hz, 1H), 6.28 (s, 1H), 5.12 - 4.40 (m, 2H), 4.23 (s, 2H), 3.90 (s, 2H), 2.74 (d, J = 6.9 Hz, 1H), 1.69 (d, J = 8.6 Hz, 1H), 1.47 (s, 2H), 1.37 (s, 2H), 1.34 (s, 4H), 1.25 (d, J = 12.4 Hz, 1H), 0.57- 0.50 (m, 2H). LC/MS (ESI) m/z: 575 $[\text{M}+\text{H}]^+$.
Example 88	 (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.71 (s, 1H), 7.96 (s, 1H), 7.67 (t, J = 52.9 Hz, 1H), 6.71 (s, 1H), 4.78 - 4.50 (m, 3H), 4.32 - 4.07 (m, 3H), 3.78 - 3.37 (m, 3H), 3.07 - 2.87 (m, 2H), 1.50 - 1.22 (m, 9H), 0.91 - 0.78 (m, 2H), 0.66 - 0.49 (m, 2H). LC/MS (ESI) (m/z): 582 $[\text{M}+\text{H}]^+$.

Example 89	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxy-4-(trifluoromethyl)piperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 9.47 (s, 1H), 8.08 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.72 (s, 1H), 6.13 (s, 1H), 3.70 (d, <i>J</i> = 11.2 Hz, 2H), 3.20 - 3.12 (m, 2H), 2.08 - 2.00 (m, 2H), 1.85 (d, <i>J</i> = 13.1 Hz, 2H), 1.51 - 1.45 (m, 2H), 1.42 - 1.35 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 564 [M+H]⁺.
Example 90	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-fluoro-4-(hydroxymethyl)piperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.49 (s, 1H), 8.05 (s, 1H), 7.69 (t, <i>J</i> = 53.1 Hz, 1H), 6.72 (s, 1H), 5.16 - 5.06 (m, 1H), 3.66 (d, <i>J</i> = 11.4 Hz, 2H), 3.56 - 3.48 (m, 2H), 3.21 - 3.12 (m, 2H), 2.02 - 1.88 (m, 4H), 1.54 - 1.46 (m, 2H), 1.42 - 1.35 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 528 [M+H]⁺.
Example 91	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-methylcyclopropane-1-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.42 (s, 1H), 7.99 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.67 (s, 1H), 4.01 - 3.95 (m, 2H), 3.46 - 3.43 (m, 2H), 3.22 - 3.20 (m, 2H), 1.49 - 1.44 (m, 2H), 1.41 - 1.35 (m, 2H), 1.27 - 1.24 (m, 5H), 1.02 - 0.99 (m, 2H), 0.91 - 0.89 (m, 2H), 0.58 - 0.54 (m, 2H). LC/MS (ESI) <i>m/z</i>: 589 [M+H]⁺.
Example 92	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-methylcyclopropane-1-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.52 (s, 1H), 9.40 (s, 1H), 8.14 (s, 1H), 7.74 (t, <i>J</i> = 54.0 Hz, 1H), 6.40 (s, 1H), 4.59 (s, 1H), 4.36 (s, 1H), 4.06 (d, <i>J</i> = 7.2 Hz, 1H), 3.88 (d, <i>J</i> = 9.3 Hz, 1H), 3.63 (d, <i>J</i> = 9.1 Hz, 1H), 3.51 (d, <i>J</i> = 14.8

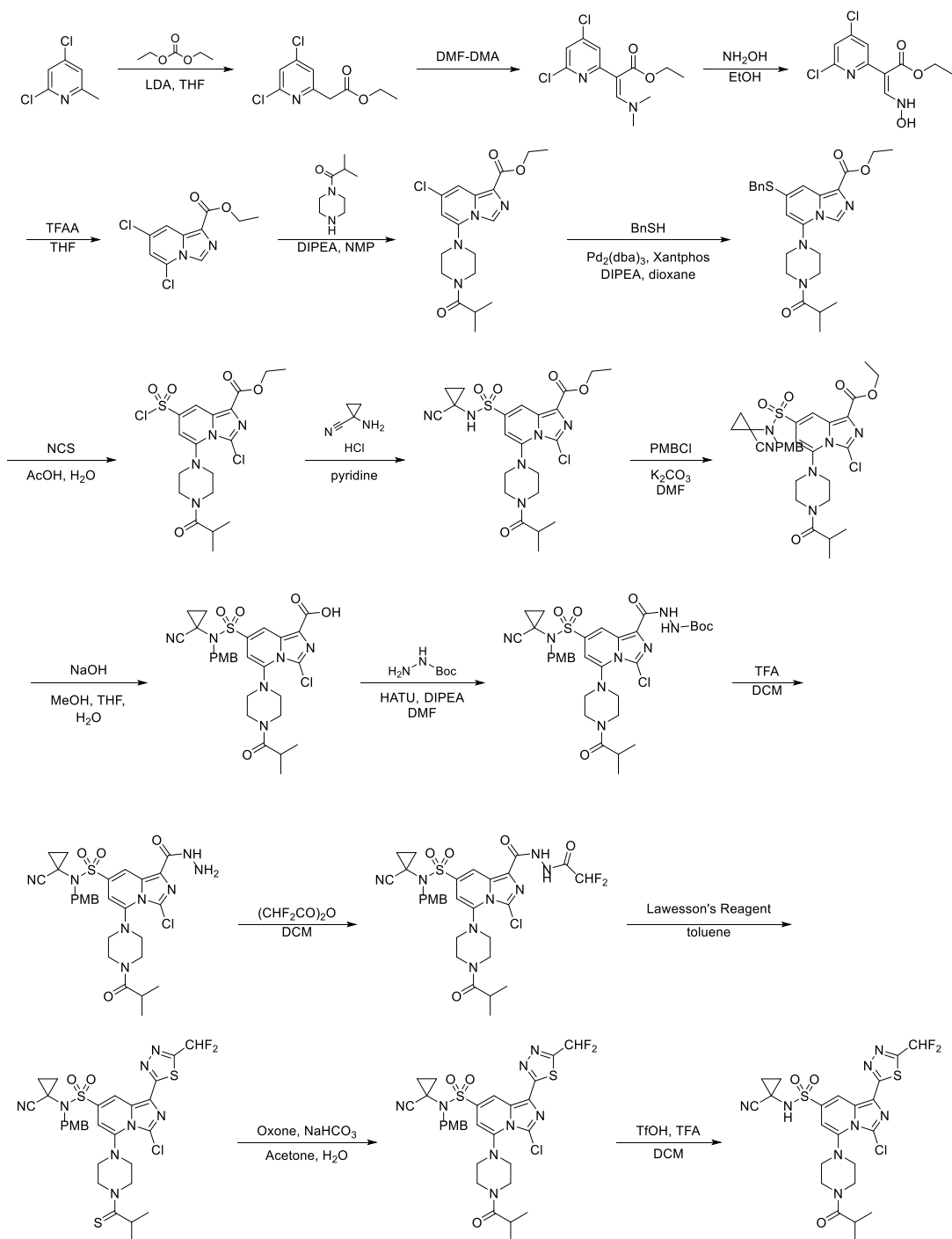
	ethyl)-1,3,4-thiadiazol-2-yl)-8-(5-(1-methylcyclopropane-1-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	Hz, 1H), 2.27 - 2.20 (m, 1H), 2.05 (s, 1H), 1.95 - 1.87 (m, 2H), 1.47 (s, 2H), 1.39 (s, 2H), 1.27 (s, 3H), 0.88 - 0.85 (m, 2H), 0.58 - 0.56 (m, 2H). LC/MS (ESI) (m/z): 589 [M+H] ⁺ .
Example 93	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-2,5-dimethyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.68 (s, 1H), 9.47 (s, 1H), 8.14 (s, 1H), 7.68 (t, <i>J</i> = 53.3 Hz, 1H), 6.62 (s, 1H), 4.80 - 4.66 (m, 1H), 4.42 - 4.30 (m, 1H), 4.14 - 3.99 (m, 1H), 3.58 - 3.51 (m, 1H), 3.40 - 3.34 (m, 1H), 3.19 - 3.12 (m, 1H), 1.53 - 1.22 (m, 10H), 0.97 (s, 3H), 0.88 - 0.81 (m, 2H), 0.64 - 0.55 (m, 2H). LC/MS (ESI) (m/z): 591 [M+H] ⁺ .
Example 94	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(2-fluoro-2-methylpropanoyl)-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.68 (s, 1H), 9.49 (s, 1H), 8.01 (s, 1H), 7.76 (d, <i>J</i> = 53.1 Hz, 1H), 6.67 (s, 1H), 4.77 - 4.71 (m, 1H), 4.39 - 4.27 (m, 1H), 3.81 - 3.67 (m, 3H), 3.14 - 3.10 (m, 1H), 3.04 - 2.89 (m, 1H), 1.64 - 1.61 (m, 3H), 1.58 - 1.55 (m, 3H), 1.52 - 1.47 (m, 3H), 1.40 - 1.36 (m, 4H). LC/MS (ESI) (m/z): 583 [M+H] ⁺ .
Example 95	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3,3-dimethyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.56 (s, 1H), 9.39 (s, 1H), 8.18 (s, 1H), 7.68 (t, <i>J</i> = 52.7 Hz, 1H), 6.43 (s, 1H), 4.10 - 4.06 (m, 2H), 3.85 - 3.81 (m, 2H), 3.67 - 3.64 (m, 2H), 1.50 - 1.47 (m, 2H), 1.45 (s, 6H), 1.39 - 1.36 (m, 2H), 1.27 (s, 3H), 0.88 - 0.85 (m, 2H), 0.58 - 0.55 (m, 2H). LC/MS (ESI) (m/z):

	l)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	591 [M+H] ⁺ .
Example 96	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-isopropyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.69 (s, 1H), 9.47 (s, 1H), 8.02 (s, 1H), 7.69 (t, <i>J</i> = 53.3 Hz, 1H), 6.75 (s, 1H), 4.34 - 4.21 (m, 2H), 3.90 - 3.83 (m, 1H), 3.79 - 3.71 (m, 1H), 3.69 - 3.58 (m, 1H), 2.98 - 2.88 (m, 2H), 2.41 - 2.32 (m, 1H), 1.51 - 1.47 (m, 2H), 1.43 - 1.38 (m, 2H), 1.30 (s, 3H), 1.24 - 1.22 (m, 1H), 0.99 - 0.94 (m, 3H), 0.87 - 0.83 (m, 2H), 0.80 - 0.77 (m, 2H), 0.67 - 0.62 (m, 1H), 0.60 - 0.55 (m, 1H). LC/MS (ESI) (<i>m/z</i>): 605 [M+H] ⁺ .
Example 97	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-isobutyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.68 (s, 1H), 9.48 (s, 1H), 7.97 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.70 (s, 1H), 4.70 (s, 1H), 4.33 - 4.23 (m, 1H), 3.76 - 3.65 (m, 3H), 3.03 - 2.92 (m, 2H), 2.02 - 1.89 (m, 1H), 1.56 - 1.35 (m, 7H), 1.30 - 1.26 (m, 2H), 0.96 - 0.89 (m, 6H), 0.87 - 0.83 (m, 2H), 0.67 - 0.61 (m, 1H), 0.59 - 0.52 (m, 1H). LC/MS (ESI) (<i>m/z</i>): 619 [M+H] ⁺ .

Example

98:

3-chloro-N-(1-cyanocyclopropyl)-1-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-7-sulfonamide



Step 1: Preparation of ethyl 2-(4,6-dichloropyridin-2-yl)acetate

At -78°C , the lithium bis(trimethylsilyl)amide solution (210 mL, 210 mmol, 1M in THF) was dropwise added slowly to the solution of 2,4-dichloro-6-methylpyridine (17 g, 104.9 mmol) in tetrahydrofuran (170 mL). The reaction mixture was stirred at -78°C for 30 minutes; and then, dimethyl carbonate (25.4 mL, 209.8 mmol) was dropwise added. After dropwise addition, the reaction mixture was stirred at -78°C for one hour. The saturated ammonium chloride solution was dropwise added slowly to quench the reaction mixture, which was then extracted with ethyl acetate for liquid separation. The organic phase was washed

saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow oil, 24 g, yield: 92.8%). ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 6.1 Hz, 2H), 4.24 - 4.17 (m, 2H), 3.80 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). LC/MS (ESI) (*m/z*): 234 [M+H]⁺.

Step 2: Preparation of ethyl (Z)-2-(4,6-dichloropyridin-2-yl)-3-(dimethylamino)acrylate

2-(4,6-dichloropyridin-2-yl) ethyl acetate (25 g, 0.427 mmol) was dissolved in N,N-dimethylformamide dimethylacetal (100 mL); and the reaction mixture was heated and stirred at 80°C for 12 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain a crude title compound (brown-yellow solid, 30 g, yield: 97.2%), which was directly used in the next step of reaction. LC/MS (ESI) (*m/z*): 289 [M+H]⁺.

Step 3: Preparation of ethyl (Z)-2-(4,6-dichloropyridin-2-yl)-3-(hydroxyamino)acrylate

Hydroxylamine hydrochloride (14.4 g, 207.5 mmol) was added to the solution of (Z)-2-(4,6-dichloropyridin-2-yl)-3-(dimethylamino)ethyl acrylate (30 g, 103.8 mmol) in tetrahydrofuran (300 mL) and methanol (60 mL). The reaction mixture was stirred at room temperature for 1 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the title compound (yellow oil, 25 g, yield: 86.9%). LC/MS (ESI) *m/z*: 277 [M+H]⁺.

Step 4: Preparation of ethyl 5,7-dichloroimidazo[1,5-a]pyridine-1-carboxylate

At 0°C, trifluoroacetic anhydride (9.47 g, 45.1 mmol) was dropwise added to the solution of (Z)-2-(4,6-dichloropyridin-2-yl)-3-(hydroxylamino)ethyl acrylate (12.5 g, 45.1 mmol) in tetrahydrofuran (125 mL). The reaction mixture was stirred overnight at room temperature. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 5 g, yield: 42.8%). ¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 1H), 8.17 (d, *J* = 2.1 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). LC/MS (ESI) *m/z*: 259 [M+H]⁺.

Step 5: Preparation of ethyl 7-chloro-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-1-carboxylate

1-(2-methylacetyl)piperazine (3.01 g, 19.3 mmol) and N,N-diisopropylethylamine (9.6 mL, 57.9 mmol) were sequentially added to the solution of 5,7-dichloroimidazo[1,5-a]pyridin-1-ethyl formate (5 g, 19.3 mmol) in N-methyl pyrrolidone (50 mL). The reaction mixture was stirred at 120°C for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and

concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (4 g, white solid, yield: 54.72%). ¹H NMR (400 MHz, CDCl₃) δ 8.39 (s, 1H), 7.88 (d, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.92 (br, 2H), 3.81 (br, 2H), 3.50 (br, 2H), 3.40 (br, 2H), 2.90 - 2.80 (m, 1H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 6H). LC/MS (ESI) *m/z*: 379 [M+H]⁺.

Step 6: Preparation of ethyl 7-(benzylthio)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-1-carboxylate

N,N-diisopropylethylamine (2.3 mL, 13.8 mmol), 4,5-biphenylphosphino-9, 9-dimethylxanthene (0.53 g, 0.92 mmol), tris(dibenzylideneacetone)dipalladium (0.85 g, 0.92 mmol) were sequentially added to the solution of 7-chloro-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5a]pyridin-1-ethyl formate (3.5 g, 9.2 mmol) and benzyl mercaptane (1.6 mL, 13.8 mmol) in 1,4-dioxane (35 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 115°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow oil, 3.5 g, yield: 81.4%). LC/MS (ESI) *m/z*: 467 [M+H]⁺.

Step 7: Preparation of ethyl 3-chloro-7-(chlorosulfonyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-1-carboxylate

At 0°C, water (2 mL) was added to the solution of 7-(benzylthio)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5a]pyridin-1-ethyl formate (1 g, 2.1 mmol) in glacial acetic acid (6 mL); and then, N-chlorosuccinimide (1.7 g, 12.6 mmol) was added portionwise. The reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow oil, 1 g, yield: 97.8%). LC/MS (ESI) *m/z*: 477 [M+H]⁺.

Step 8: Preparation of ethyl 3-chloro-7-(N-(1-cyanocyclopropyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-1-carboxylate

At 0°C, 3-chloro-7-(sulfonyl chloride)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5a]pyridin-1-ethyl formate (500 mg, 4.2 mmol) was added portionwise to the solution of 1-amino-1-cyclopropyl cyanic hydrochloride (1 g, 2.1 mmol) in pyridine (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, ice water was added for quenching; the reaction mixture was extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: ethyl

acetate/petroleum ether, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 680 mg, yield: 62.1%). LC/MS (ESI) m/z: 523 [M+H]⁺.

Step 9: Preparation of ethyl 3-chloro-7-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-1-carboxylate

Potassium carbonate (539 mg, 3.9 mmol) and p-methoxybenzyl chloride (305 mg, 2.0 mmol) were sequentially added to the solution of 3-chloro-7-(N-(1-cyanocyclopropyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5a]pyridin-1-ethyl formate (680 mg, 1.3 mmol) in N,N-dimethylformamide (7 mL). The reaction mixture was stirred at 45°C for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 700 mg, yield: 83.7%). LC/MS (ESI) m/z: 643 [M+H]⁺.

Step 10: Preparation of 3-chloro-7-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-1-carboxylic acid

At 0°C, sodium hydroxide (43.5 mg, 1.1 mmol) was added to the mixed solution of 3-chloro-7-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5a]pyridin-1-ethyl formate (350 mg, 0.54 mmol) in methanol (2 mL), tetrahydrofuran (1 mL) and water (1 mL); and the reaction mixture was stirred at 45°C for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, acidified to pH-5 with 1N hydrochloric acid, and extracted with ethyl acetate twice. The organic phase was combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow solid, 320 mg, yield: 97.0%). LC/MS (ESI) m/z: 615 [M+H]⁺.

Step 11: Preparation of tert-butyl 2-(3-chloro-7-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-1-carbonyl)hydrazine-1-carboxylate

Diisopropylethylamine (202 mg, 1.56 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (218 mg, 0.57 mmol) were sequentially added to the solution of 3-chloro-7-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5a]pyridin-1-formic acid (320 mg, 0.52 mmol) and tert-butyl hydrazinoformate (76 mg, 0.57 mmol) in N,N-dimethylformamide (4 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced

pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 330 mg, yield: 86.8%). LC/MS (ESI) m/z: 729 [M+H]⁺.

Step

12:

3-chloro-N-(1-cyanocyclopropyl)-1-(hydrazinecarbonyl)-5-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-7-sulfonamide

At 0°C, trifluoroacetic acid (1.5 mL) was dropwise added to the solution of 2-(3-chloro-7-(N-(1-cyanocyclopropyl)-N-(4-methoxybenzyl)sulfamoyl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridin-1-carbonyl)hydrazin-1-tert-butyl formate (330 mg, 0.45 mmol) in dichloromethane (4 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain a crude title compound (yellow oil, 285 mg, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) m/z: 629 [M+H]⁺.

Step

13:

Preparation

of

3-chloro-N-(1-cyanocyclopropyl)-1-(2-(2,2-difluoroacetyl)hydrazine-1-carbonyl)-5-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-7-sulfonamide

At 0°C, difluoroacetic anhydride (79 mg, 0.45 mmol) was dropwise added to the solution of 3-chloro-N-(1-cyanocyclopropyl)-1-(hydrazinocarbonyl)-5-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridin-7-sulfonamide (285 mg, 0.45 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, sequentially washed with saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 240 mg, yield: 75%). LC/MS (ESI) m/z: 707 [M+H]⁺.

Step

14:

Preparation

of

3-chloro-N-(1-cyanocyclopropyl)-1-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-5-(4-(2-methylpropanethioyl)piperazin-1-yl)imidazo[1,5-a]pyridine-7-sulfonamide

The Lawesson's reagent (151 mg, 0.37 mmol) was added to the solution of 3-chloro-N-(1-cyanocyclopropyl)-1-(2-(2,2-difluoroacetyl)hydrazin-1-carbonyl)-5-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridin-7-sulfonamide (240 mg, 0.34 mmol) in toluene (3 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 110°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the

title compound (yellow solid, 125 mg, yield: 71.0%). LC/MS (ESI) m/z: 721 [M+H]⁺.

Step

15:

3-chloro-N-(1-cyanocyclopropyl)-1-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-5-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-7-sulfonamide

At 0°C, water (0.2 mL), sodium bicarbonate (80 mg, 0.95 mmol) and Oxone (70 mg, 0.12 mmol) were sequentially added to the solution of 3-chloro-N-(1-cyanocyclopropyl)-1-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-5-(4-(2-methylpropylthio)piperazin-1-yl)imidazo[1,5-a]pyridine-7-sulfonamide (180 mg, 0.25 mmol) in acetone (2 mL). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine respectively, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the title compound (yellow solid, 125 mg, yield: 71.0%). LC/MS (ESI) m/z: 705 [M+H]⁺.

Step

16:

Preparation

of

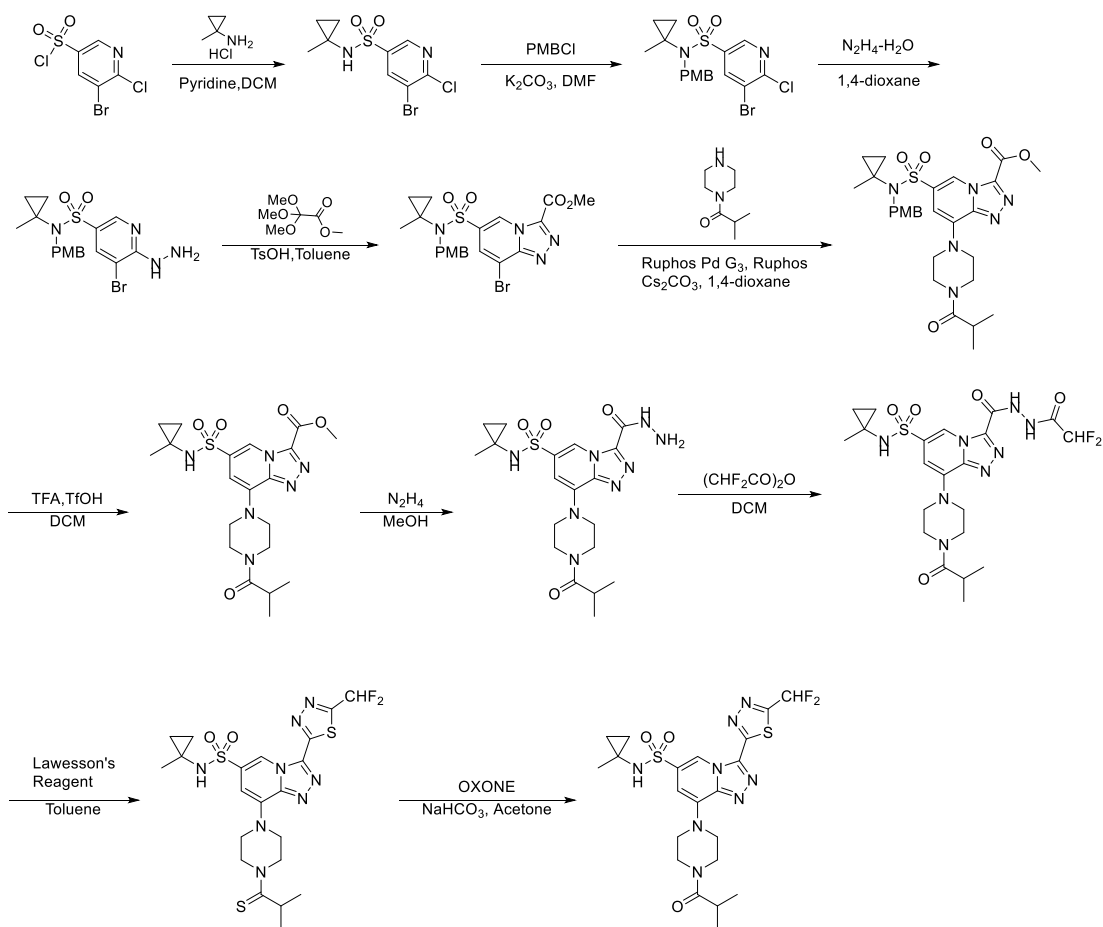
3-chloro-N-(1-cyanocyclopropyl)-1-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-5-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-7-sulfonamide

At 0°C, trifluoroacetic acid (0.5 mL) and trifluoromethanesulfonic acid (0.1 mL) were sequentially added to the solution of 3-chloro-N-(1-cyanocyclopropyl)-1-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-5-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-7-sulfonamide (40 mg, 0.057 mmol) in dichloromethane (0.5 mL); and then, the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the mixture was concentrated to dryness, and the residue was purified by pre-HPLC to obtain the title compound (white solid, 5.5 mg, yield: 16.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.74 (s, 1H), 9.01 (s, 1H), 8.81 (s, 1H), 7.67 (t, *J* = 53.3 Hz, 1H), 3.83 - 3.38 (m, 8H), 3.00 - 2.91 (m, 1H), 1.50 - 1.45 (m, 2H), 1.37 - 1.31 (m, 2H), 1.05 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 585 [M+H]⁺.

Example

99:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide



Step 1: 5-bromo-6-chloro-N-(1-methylcyclopropyl)pyridine-3-sulfonamide

At 0°C, the solution of 5-bromo-6-chloropyridin-3-sulfonyl chloride (1.5 g, 5.2 mmol) in dichloromethane (5 mL) was dropwise added slowly to the solution of 1-methylcyclopropan-1-amine (1 g, 10 mmol) in pyridine (10 mL). The reaction mixture was stirred at room temperature for 1 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (white solid, 1.2 g, yield: 71.5%). ¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1H), 8.29 (s, 1H), 4.99 (s, 1H), 1.25 (s, 3H), 0.75 - 0.68 (m, 2H), 0.56 - 0.47 (m, 2H). LC/MS (ESI) m/z: 326 [M+H]⁺.

Step 2: 5-bromo-6-chloro-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)pyridine-3-sulfonamide

Potassium carbonate (1.0 g, 7.4 mmol) and 1-(chloromethyl)-4-methoxybenzene (0.9 g, 5.7 mmol) were sequentially added to the solution of 5-bromo-6-chloro-N-(1-methylcyclopropyl)pyridin-3-sulfonamide (1.2 g, 3.7 mmol) in N,N-dimethylformamide (10 mL). The reaction mixture was stirred at 50°C for 2 hours. The mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (white solid, 1.4 g, yield: 85.2%). ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 7.69 (s, 1H),

7.06 (d, $J = 7.7$ Hz, 2H), 6.71 (d, $J = 7.8$ Hz, 2H), 4.39 (s, 2H), 3.73 (s, 3H), 1.24 (s, 3H), 0.89 - 0.82 (m, 2H), 0.68 - 0.61 (m, 2H). LC/MS (ESI) m/z : 446 $[M+H]^+$.

Step 3: 5-bromo-6-hydrazineyl-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)pyridine-3-sulfonamide

Hydrazine hydrate (0.6 g, 12.0 mmol) was dropwise added slowly to the solution of 5-bromo-6-chloro-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)pyridin-3-sulfonamide (1.3 g, 2.9 mmol) in 1,4-dioxane (13 mL). The reaction mixture was stirred at 50°C for 2 hours. The mixture was diluted with dichloromethane, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the title compound (colorless oil, 0.9 g, yield: 69.9%). LC/MS (ESI) m/z : 441 $[M+H]^+$.

Step 4: Methyl 8-bromo-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfamoyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

2,2-trimethoxymethyl acetate (1.7 g, 10 mmol) and p-toluenesulfonic acid (0.4 g, 0.2 mmol) were sequentially added to the solution of 5-bromo-6-hydrazino-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)pyridin-3-sulfonamide (0.9 g, 2.0 mmol) in toluene (15 mL). The reaction mixture was stirred at 85°C for 2 hours. The mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 870 mg, yield: 83.8%). ^1H NMR (400 MHz, CDCl_3) δ 9.10 (s, 1H), 7.39 (s, 1H), 7.00 (d, $J = 8.1$ Hz, 2H), 6.55 (d, $J = 8.1$ Hz, 2H), 4.44 (s, 2H), 4.07 (s, 3H), 3.56 (s, 3H), 1.35 (s, 3H), 0.90 - 0.76 (m, 2H), 0.61 - 0.47 (m, 2H). LC/MS (ESI) m/z : 509 $[M+H]^+$.

Step 5: Methyl 8-(4-isobutyrylpiperazin-1-yl)-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfamoyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

Cesium carbonate (260 mg, 0.8 mmol), RuPhos (25 mg, 0.05 mmol) and RuPhos Pd G3 (25 mg, 0.03 mmol) were sequentially added to the solution of 8-bromo-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfamoyl)-[1,2,4]triazolo[4,3-a]pyridin-3-methyl carboxylate (135 mg, 0.26 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (60 mg, 0.4 mmol) in 1,4-dioxane (5 mL). The reaction mixture was stirred at 110°C for 3 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-100% ethyl acetate) to obtain the title compound (yellow solid, 79 mg, yield: 52.9%). LC/MS (ESI) m/z : 585 $[M+H]^+$.

Step 6: Methyl

8-(4-isobutyrylpiperazin-1-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

At 0°C, trifluoroacetic acid (70 mg, 0.6 mmol) and trifluoromethanesulfonic acid (30 mg, 0.2 mmol) were sequentially added to the solution of 8-(4-isobutyrylpiperazin-1-yl)-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfamoyl)-[1,2,4]triazolo[4,3-a]pyridin-3-methyl carboxylate (70 mg, 0.12mmol) in dichloromethane (1 mL); and then, the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was alkalinized to pH-7 with saturated sodium bicarbonate solution, and extracted with ethyl acetate twice. The organic phase was combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow solid, 45 mg, yield: 80%). LC/MS (ESI) (m/z): 465 [M+H]⁺.

Step **7:**

3-(hydrazinecarbonyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

Hydrazine hydrate (56 mg, 1.0 mmol) was dropwise added slowly to the solution of 8-(4-isobutyrylpiperazin-1-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)-[1,2,4]triazolo[4,3-a]pyridin-3-methyl carboxylate (45 mg, 0.1mmol) in methanol (1 mL); and then, the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (yellow solid, 40 mg, yield: 88.9%). LC/MS (ESI) (m/z): 465 [M+H]⁺.

Step **8:**

3-(2-(2,2-difluoroacetyl)hydrazine-1-carbonyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

At 0°C, difluoroacetic anhydride (18 mg, 0.11 mmol) was slowly added to the solution of 3-(hydrazinocarbonyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-6-sulfonamide (40 mg, 0.9 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution and saturated brine respectively, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 35 mg, yield: 74.9%). LC/MS (ESI) (m/z): 543 [M+H]⁺.

Step **9:**

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(4-(2-methylpropanethioyl)piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

The Lawesson's reagent (52 mg, 0.13 mmol) was added to the solution of 3-(2-(2,2-difluoroacetyl)hydrazin-1-carbonyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]t

riazolo[4,3-a]pyridin-6-sulfonamide (30 mg, 0.08 mmol) in toluene (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 110°C for 4 hours under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-100% ethyl acetate) to obtain the title compound (yellow solid, 15 mg, yield: 30%). LC/MS (ESI) (m/z): 559 [M+H]⁺.

Step

10:

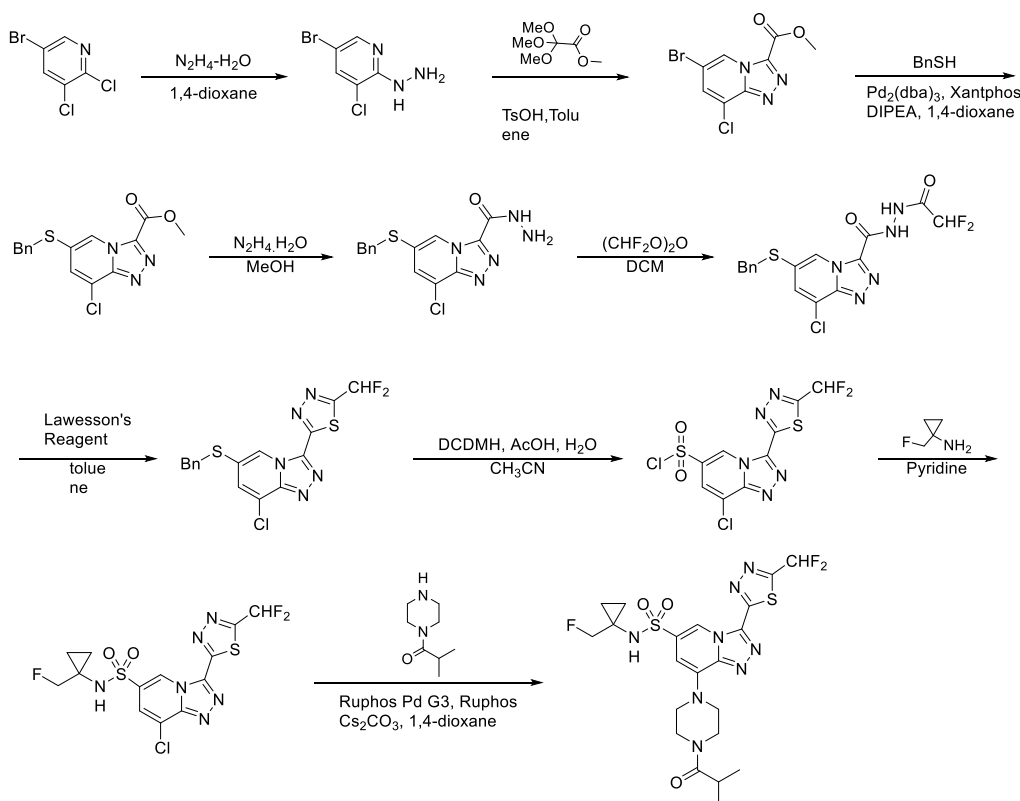
3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

At 0°C, water (0.1 mL), sodium bicarbonate (15 mg, 0.1 mmol) and potassium hydrogen persulfate (18 mg, 0.03 mmol) were sequentially added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(4-(2-methylpropionyl)piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide (15 mg, 0.03 mmol) in acetone (1 mL). The reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 0.7 mg, yield: 4.8%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.34 (s, 1H), 8.52 (s, 1H), 7.75 (t, *J* = 53.2 Hz, 1H), 6.92 (s, 1H), 3.83 - 3.77 (m, 4H), 3.76 - 3.68 (m, 4H), 3.02 - 2.91 (m, 1H), 1.16 (s, 3H), 1.06 - 1.03 (m, 6H), 0.75 - 0.70 (m, 2H), 0.50 - 0.42 (m, 2H).

Example

100:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide



Step 1: 5-bromo-3-chloro-2-hydrazinopyridine

At room temperature, hydrazine hydrate (80 mL, 80% wt.) was added to the solution of 5-bromo-2,3-dichloropyridine (20 g, 88.1 mmol) in ethanol (200 mL); and the reaction mixture was stirred at 100°C for 34 hours. After completion of the reaction, water was added; the reaction mixture was extracted with dichloromethane; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 16 g, yield: 82.0%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z) 223 $[M+H]^+$.

Step 2: Methyl 6-bromo-8-chloro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

At room temperature, p-toluenesulfonic acid (2.7 g, 19.9 mmol) and 2,2,2-trimethoxymethyl acetate (25 g, 149 mmol) were added to the solution of 5-bromo-3-chloro-2-hydrazinopyridine (11 g, 49.7 mmol) in toluene (150 mL). The reaction mixture was stirred at 80°C for 12 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (ethyl acetate/petroleum ether = 1/2) to obtain the title compound (white solid, 10.8 g, yield: 78%). ^1H NMR (400 MHz, CDCl_3) δ 9.22 (d, J = 1.4 Hz, 1H), 7.57 (d, J = 1.4 Hz, 1H), 4.06 (s, 3H). LC/MS (ESI) (m/z): 291 $[M+H]^+$.

Step 3: Methyl 6-(benzylthio)-8-chloro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

Under an atmosphere of nitrogen at room temperature, N,N-diisopropylethylamine (16.6 mL, 92.8 mmol),

Xantphos (4.5 g, 7.42 mmol), Pd₂(dba)₃ (3.3 g, 3.71 mmol) and benzyl mercaptane (4.7 g, 37.1 mmol) were sequentially added to the solution of 6-bromo-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-methyl carboxylate (10.8 g, 37.1 mmol) in 1,4-dioxane (100 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (ethyl acetate/petroleum ether = 1/2) to obtain the title compound (yellow solid, 12 g, yield: 97%). LC/MS (ESI) (m/z): 334 [M+H]⁺.

Step 4: 6-(benzylthio)-8-chloro-[1,2,4]triazolo[4,3-a]pyridine-3-carbohydrazide

At room temperature, hydrazine hydrate (12.8 mL, 80% wt.) was added to the solution of 6-(benzylthio)-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-methyl carboxylate (12 g, 35.9 mmol) in methanol (200 mL). The reaction mixture was stirred at 25°C for 12 hour. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; and the residue was pulped with the mixed solution of petroleum ether/ethyl acetate, and dried in vacuum to obtain a crude title compound (yellow solid, 20 g, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 334 [M+H]⁺.

Step 5: 6-(benzylthio)-8-chloro-N'-(2,2-difluoroacetyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carbohydrazide

At 0°C, difluoroacetic anhydride (15.6 g, 53.9 mmol) was added to the solution of 6-(benzylthio)-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-carbohydrazide (20 g, 35.9 mmol) in dichloromethane (200 mL). The reaction mixture was stirred at 25°C for 0.5 hour. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (ethyl acetate/petroleum ether = 1/2) to obtain the title compound (yellow solid, 14 g, yield: 99%). LC/MS (ESI) (m/z): 412 [M+H]⁺.

Step

6:

2-(6-(benzylthio)-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

Under an atmosphere of nitrogen at 0°C, the Lawesson's reagent (15.6 g, 39.5 mmol) was added to the solution of 6-(benzylthio)-8-chloro-N'-(2,2-difluoroacetyl)-[1,2,4]triazolo[4,3-a]pyridin-3-formylhydrazine (14 g, 35.9 mmol) in toluene (150 mL); and the reaction mixture was stirred at 110°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (ethyl acetate/petroleum ether = 1/2) to obtain the title compound (white solid, 4.5g, yield: 31%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.09 (d, *J* = 1.4 Hz, 1H), 8.00 (d, *J* = 1.4 Hz, 1H), 7.89-7.58 (m, 1H), 7.42-7.37 (m, 2H), 7.33-7.28 (m, 2H), 7.25-7.20 (m, 1H), 4.38 (s, 2H). LC/MS (ESI) (m/z): 410 [M+H]⁺.

Step 7: 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonyl chloride

At 0°C, dichlorohydantoin (1.65 g, 8.4 mmol) was added portionwise to 2-(6-(benzylthio)-8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (1.1 g, 2.8 mmol) in the mixed solution of acetonitrile (8 mL), water (2 mL) and 1N dilute hydrochloric acid (2 mL). The reaction mixture was stirred at 0°C for one hour. After completion of the reaction, the reaction mixture was diluted with dichloromethane, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude title compound (white solid, 2.8 g, yield: 100%), which was directly used in the next step of reaction without purification. LC/MS (ESI) (m/z): 386 [M+H]⁺.

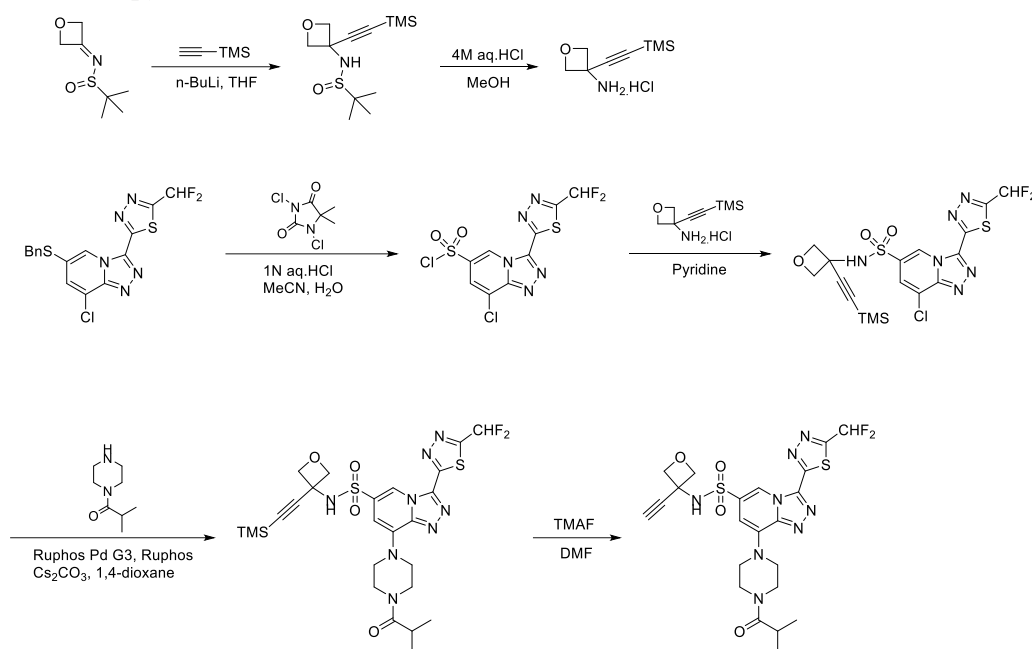
Step 8: 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

At 0°C, triethylamine (273 mg, 2.73 mmol) and 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonyl chloride (350 mg, 0.91 mmol) were added to the solution of 1-(fluoromethyl)cyclopropan-1-amine (117 mg, 1.35 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at 0°C for one hour. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (ethyl acetate/petroleum ether= 1/3) to obtain the title compound (white solid, 220 mg, yield: 55%). LC/MS (ESI) (m/z): 410 [M+H]⁺.

Step 9: 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (67 mg, 0.20 mmol), Ruphos (7 mg, 0.028 mmol), Ruphos Pd G3 (7 mg, 0.014 mmol) were sequentially added to the solution of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide (60 mg, 0.137 mmol) and 1-(2-methylacetyl)-piperazine (25.6 mg, 0.164 mmol) in 1,4-dioxane (2 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was filtered; the filtrate was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 1.7 mg, yield: 2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.32 (s, 1H), 8.91 (s, 1H), 7.68 (d, *J* = 53.0 Hz, 1H), 6.93 (s, 1H), 4.29 (s, 1H), 4.17 (s, 1H), 3.80-3.69 (m, 8H), 2.99-2.95 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 6H), 0.87-0.84 (m, 2H), 0.80-0.76 (m, 2H). LC/MS (ESI) (m/z): 559 [M+H]⁺.

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-ethynyloxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide



Step 1: 3-[(tert-butylsulfinyl)amino]-3-[(trimethylsilyl)acetynyl]oxacyclobutane

Under an atmosphere of nitrogen at -78°C , the solution of 2.5M n-butyl lithium (3.2 mL, 8.0 mmol) in n-hexane was dropwise added slowly to the solution of acetynyltrimethylsilane (840 mg, 8.5 mmol) in tetrahydrofuran (10 mL). After dropwise adding, the reaction mixture was stirred at -78°C for 30 minutes. The solution of 3-[(tert-butylsulfinyl)imino]oxacyclobutane (1 g, 5.7 mmol) in tetrahydrofuran (5 mL) was slowly added to the above reaction mixture. After dropwise adding, with the temperature kept at -78°C , the mixture was stirred for 10 minutes. After completion of the reaction, with the temperature slowly rising to 0°C , the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-40% ethyl acetate) to obtain the title compound (yellow liquid, 1.2 g, yield: 76.9%). LC/MS (ESI) (m/z): 274 $[\text{M}+\text{H}]^{+}$.

Step 2: 3-[(trimethylsilyl)ethynyl]oxetan-3-amine hydrochloride

At 0°C , the solution of 4M dioxane hydrochloride (0.4 mL, 1.6 mmol) was dropwise added slowly to the solution of 3-[(tert-butylsulfinyl)amino]-3-[(trimethylsilyl)acetynyl]oxacyclobutane (300 mg, 1.1 mmol) in methanol (5 mL). The reaction mixture was stirred at 0°C for 30 minutes under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain a crude title compound (white solid, 226 mg, yield: 100%), which was directly used in the next step of reaction without purification. LC/MS (ESI) (m/z): 170 $[\text{M}+\text{H}]^{+}$.

By referring to the preparation method in Example 100, Steps 3-5 were implemented according to a similar route by starting from appropriate starting materials to obtain the target compound.

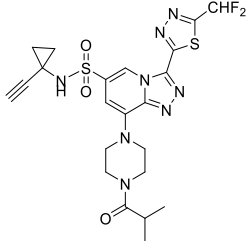
Step

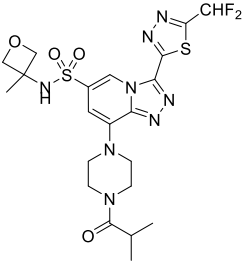
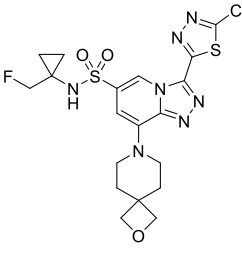
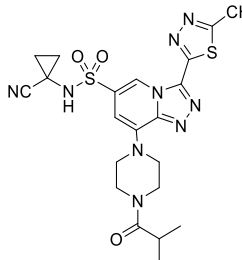
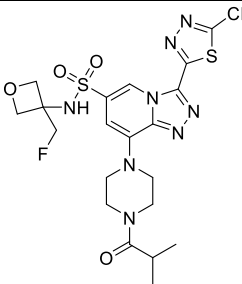
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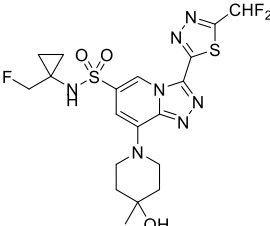
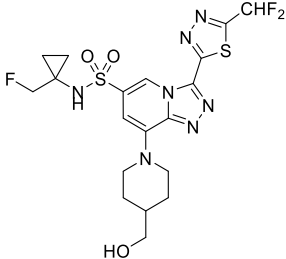
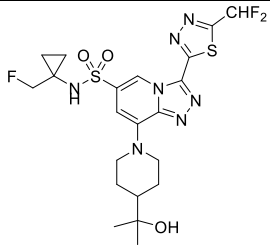
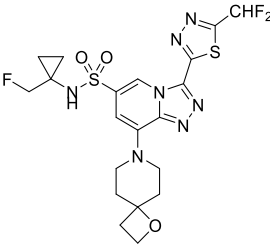
3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-ethynyloxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

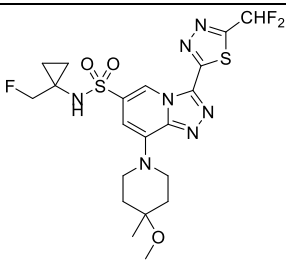
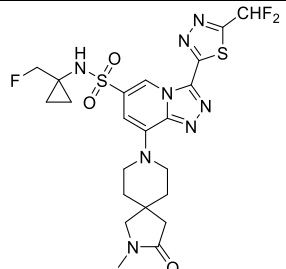
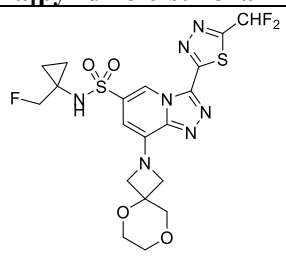
At 0°C, tetramethylammonium fluoride tetrahydrate (43 mg, 0.26 mmol) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-((trimethylsilyl)acetenyl)oxacyclobutan-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide (55 mg, 0.09 mmol) in N,N-dimethylformamide (1 mL). The reaction mixture was stirred at room temperature for one hour. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with saturated aqueous ammonium chloride solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 14.0 mg, yield: 28.7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.35 (d, *J* = 1.0 Hz, 1H), 7.91 - 7.58 (m, 1H), 6.93 (s, 1H), 4.76 (d, *J* = 6.5 Hz, 2H), 4.63 (d, *J* = 6.4 Hz, 2H), 3.83 - 3.67 (m, 8H), 3.45 (s, 1H), 3.01 - 2.93 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) *m/z*: 567 [M+H]⁺.

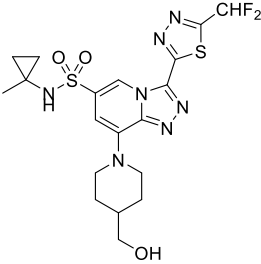
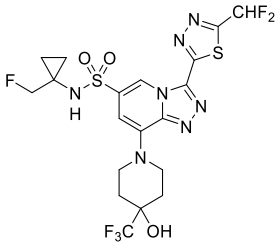
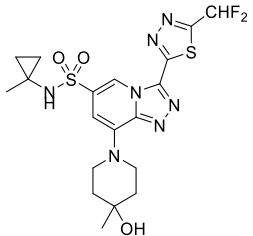
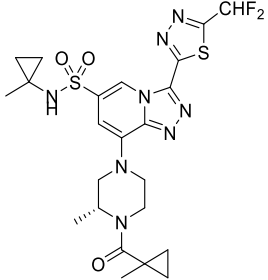
By referring to the preparation method in Example 100, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

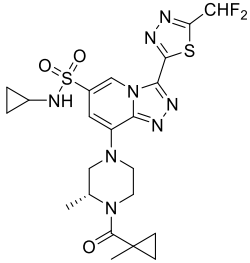
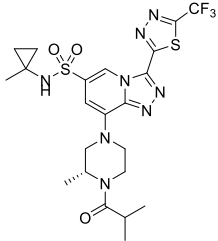
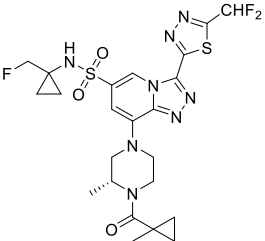
Example	Structure and name	Analysis data
Example 102	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-ethynylcyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.41 (s, 1H), 9.06 (s, 1H), 7.89 - 7.60 (m, 1H), 6.98 (s, 1H), 3.79 - 3.73 (m, 8H), 3.00 - 2.94 (m, 1H), 2.79 (s, 1H), 1.39 - 1.34 (m, 2H), 1.29 - 1.24 (m, 2H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) <i>m/z</i> : 551 [M+H] ⁺ .

Example 103	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methoxyetan-3-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.33 (d, <i>J</i> = 1.1 Hz, 1H), 8.81 (s, 1H), 7.75 (t, <i>J</i> = 53.0 Hz, 1H), 6.95 (d, <i>J</i> = 1.0 Hz, 1H), 4.63 (d, <i>J</i> = 6.2 Hz, 2H), 4.18 (d, <i>J</i> = 6.4 Hz, 2H), 3.88 - 3.78 (m, 4H), 3.76 - 3.69 (m, 4H), 3.01 - 2.93 (m, 1H), 1.49 (s, 3H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 557 [M+H]⁺.
Example 104	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.56 (s, 1H), 7.34 (t, <i>J</i> = 53.4 Hz, 1H), 7.00 (s, 1H), 4.56 - 4.53 (m, 4H), 4.27 (s, 1H), 4.14 (s, 1H), 3.72 - 3.68 (m, 4H), 2.15 - 2.12 (m, 4H), 1.02 - 0.98 (m, 2H), 0.83 - 0.81 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 530 [M+H]⁺.
Example 105	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.02 (s, 1H), 7.60 - 7.23 (m, 1H), 7.19 (s, 1H), 3.89 (s, 6H), 3.72 (s, 2H), 3.07 - 3.01 (m, 1H), 1.54 - 1.51 (m, 2H), 1.49 - 1.45 (m, 2H), 1.15 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 552 [M+H]⁺.
Example 106	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.09 (s, 1H), 9.02 (d, <i>J</i> = 1.3 Hz, 1H), 7.84 - 7.58 (m, 1H), 7.17 (d, <i>J</i> = 1.2 Hz, 1H), 4.75 (s, 1H), 4.64 - 4.60 (m, 3H), 4.37 (d, <i>J</i> = 6.9 Hz, 2H), 3.79 - 3.72 (m, 6H), 3.66 - 3.61 (m, 2H), 3.00 - 2.94 (m, 1H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 575 [M+H]⁺.

	rylpiperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	[M+H] ⁺ .
Example 107	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-hydroxy-4-methylpiperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.26 (d, <i>J</i> = 1.3 Hz, 1H), 8.88 (s, 1H), 7.74 (t, <i>J</i> = 53.1 Hz, 1H), 6.91 (s, 1H), 4.53 (s, 1H), 4.28 (s, 1H), 4.17 - 4.09 (m, 3H), 3.55 - 3.51 (m, 2H), 1.71 - 1.65 (m, 4H), 1.21 (s, 3H), 0.87 - 0.85 (m, 2H), 0.79 - 0.76 (m, 2H). LC/MS (ESI) (m/z): 518 [M+H] ⁺ .
Example 108	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-(hydroxymethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.26 (s, 1H), 8.88 (s, 1H), 7.74 (t, 1H), 6.89 (s, 1H), 4.58 - 4.54 (m, 2H), 4.51 (s, 1H), 4.28 (s, 1H), 4.16 (s, 1H), 3.09 - 3.02 (m, 3H), 1.86-1.80 (m, 3H), 1.42 - 1.30 (m, 3H), 0.87 - 0.84 (m, 2H), 0.79 - 0.76 (m, 2H). LC/MS (ESI) (m/z): 518 [M+H] ⁺ .
Example 109	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.85 (s, 1H), 7.70 (t, <i>J</i> = 53.2 Hz, 1H), 7.08 (s, 1H), 4.50 (d, <i>J</i> = 12.2 Hz, 2H), 4.29 (s, 1H), 4.20 (s, 1H), 4.16 (s, 1H), 2.94 - 2.87 (m, 2H), 1.91 - 1.85 (m, 2H), 1.53 - 1.43 (m, 3H), 1.09 (s, 6H), 0.85 - 0.81 (m, 2H), 0.79 - 0.75 (m, 2H). LC/MS (ESI) (m/z): 546 [M+H] ⁺ .
Example 110	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-(2-oxo-2,3-dihydro-1H-benzofuran-3-yl)piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.14 (s, 1H), 7.74 (t, <i>J</i> = 53.1 Hz, 1H), 6.90 (s, 1H), 4.48 - 4.43 (m, 2H), 4.22 (d, <i>J</i> = 49.3 Hz, 2H), 3.71 - 3.67 (m, 2H), 3.62 - 3.58 (m, 2H), 2.46 - 2.43 (m, 2H), 2.01 - 1.95 (m, 4H), 0.51 - 0.44 (m, 2H), 0.40 -

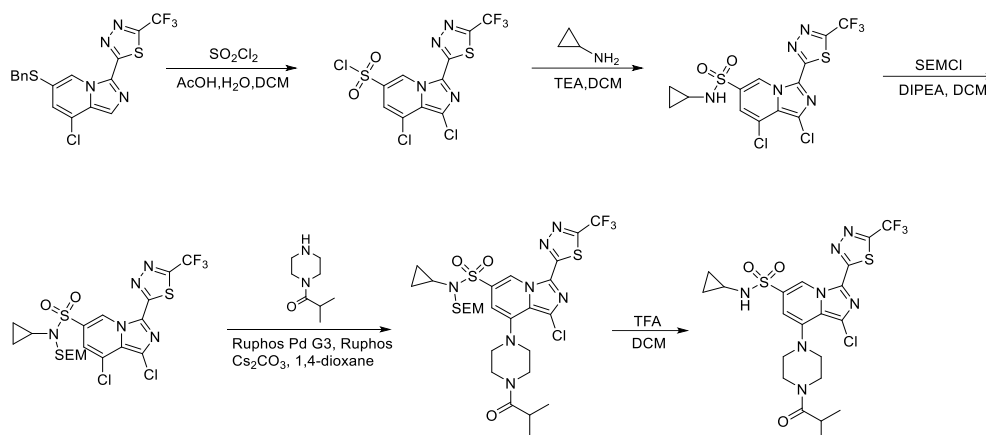
	N-(1-(fluoromethyl)cyclopropyl)-8-(1-oxa-7-azaspiro[3.5]nonan-7-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	0.32 (m, 2H). LC/MS (ESI) (m/z): 530 [M+H] ⁺ .
Example 111	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-methoxy-4-methylpiperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.27 (d, <i>J</i> = 1.1 Hz, 1H), 8.88 (s, 1H), 7.75 (t, <i>J</i> = 53.1 Hz, 1H), 6.91 (s, 1H), 4.28 (s, 1H), 4.15 (s, 1H), 4.15 - 4.08 (m, 2H), 3.44 - 3.40 (m, 2H), 3.18 (s, 3H), 1.92 - 1.85 (m, 2H), 1.75 - 1.66 (m, 2H), 1.19 (s, 3H), 0.89 - 0.83 (m, 2H), 0.81 - 0.75 (m, 2H). LC/MS (ESI) (m/z): 532 [M+H] ⁺ .
Example 112	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(2-methyl-3-oxo-2,8-diazaspiro[4.5]decan-8-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.56 (s, 1H), 7.53 - 7.27 (m, 1H), 7.01 (s, 1H), 4.27 (s, 1H), 4.15 (s, 1H), 3.89 - 3.84 (m, 2H), 3.74 - 3.68 (m, 2H), 3.41 (s, 2H), 2.87 (s, 3H), 2.43 (s, 2H), 1.94 - 1.88 (m, 4H), 1.03 - 0.99 (m, 2H), 0.93 - 0.85 (m, 2H). LC/MS (ESI) (m/z): 571 [M+H] ⁺ .
Example 113	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(5,8-dioxaspiro[3.5]nonan-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.36 (s, 1H), 7.40 (t, <i>J</i> = 53.4 Hz, 1H), 6.50 (s, 1H), 4.43 - 4.40 (m, 2H), 4.30 (s, 1H), 4.26 - 4.23 (m, 2H), 4.18 (s, 1H), 3.89 (s, 2H), 3.80 - 3.77 (m, 2H), 3.73 - 3.70 (m, 2H), 1.00 - 0.97 (m, 2H), 0.83 - 0.80 (m, 2H). LC/MS (ESI) (m/z): 532 [M+H] ⁺ .

Example 114	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(hydroxymethyl)piperidin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.29 (d, <i>J</i> = 1.1 Hz, 1H), 8.51 (s, 1H), 7.75 (t, <i>J</i> = 53.1 Hz, 1H), 6.89 (s, 1H), 4.57 - 4.54 (m, 2H), 4.54 - 4.51 (m, 1H), 3.36 - 3.34 (m, 2H), 3.10 - 3.02 (m, 2H), 1.88 - 1.82 (m, 2H), 1.77 - 1.68 (m, 1H), 1.41 - 1.31 (m, 2H), 1.16 (s, 3H), 0.76 - 0.72 (m, 2H), 0.48 - 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 500 [M+H]⁺.
Example 115	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(4-hydroxy-4-(trifluoromethyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.29 (d, <i>J</i> = 1.1 Hz, 1H), 8.88 (s, 1H), 7.74 (t, <i>J</i> = 53.0 Hz, 1H), 6.97 (d, <i>J</i> = 1.0 Hz, 1H), 6.20 (s, 1H), 4.57 - 4.42 (m, 2H), 4.27 (s, 1H), 4.15 (s, 1H), 3.31 - 3.26 (m, 2H), 1.97 - 1.82 (m, 4H), 0.90 - 0.82 (m, 2H), 0.80 - 0.74 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 572 [M+H]⁺.
Example 116	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxy-4-methylpiperidin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H), 7.12 (t, <i>J</i> = 53.2 Hz, 1H), 6.82 (s, 1H), 5.13 (s, 1H), 4.33 - 4.20 (m, 2H), 3.64 - 3.50 (m, 2H), 1.96 - 1.88 (m, 2H), 1.83 - 1.78 (m, 2H), 1.31 (s, 3H), 1.26 (d, <i>J</i> = 3.7 Hz, 3H), 0.90 - 0.88 (m, 2H), 0.62 - 0.57 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 500 [M+H]⁺.
Example 117	 (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperidin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.34 - 9.31 (m, 1H), 8.51 (s, 1H), 7.76 (t, <i>J</i> = 53.1 Hz, 1H), 6.93 (s, 1H), 4.72 - 4.70 (m, 1H), 4.55 - 4.52 (m, 1H), 4.30 (t, <i>J</i> = 13.9 Hz, 2H), 3.27 - 3.24 (m, 2H), 3.09 - 3.07 (m, 1H), 1.27 - 1.25 (m, 6H), 1.18 (s, 3H), 0.90 - 0.84 (m, 2H), 0.77 - 0.71 (m, 2H), 0.63 - 0.58 (m, 2H), 0.47 - 0.43 (m, 2H).

	arbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	2H). LC/MS (ESI) (m/z): 567 [M+H] ⁺ .
Example 118	 (R)-N-cyclopropyl-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.35 (s, 1H), 8.34 (s, 1H), 7.76 (t, <i>J</i> = 53.2 Hz, 1H), 6.94 (s, 1H), 4.72 (s, 1H), 4.54 (d, <i>J</i> = 12.0 Hz, 1H), 4.31 (t, <i>J</i> = 13.9 Hz, 2H), 3.27 - 3.24 (m, 2H), 3.11 - 3.07 (m, 1H), 2.30 - 2.28 (m, 1H), 1.34 - 1.29 (m, 6H), 0.91 - 0.83 (m, 2H), 0.62 - 0.58 (m, 2H), 0.55 - 0.50 (m, 4H). LC/MS (ESI) (m/z): 553 [M+H] ⁺ .
Example 119	 (R)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.29 (s, 1H), 8.54 (s, 1H), 6.93 (s, 1H), 4.71 (d, <i>J</i> = 55.8 Hz, 1H), 4.48 - 4.05 (m, 3H), 3.62 (s, 1H), 3.20 - 3.06 (m, 2H), 2.97 - 2.92 (m, 1H), 1.37 - 1.30 (m, 3H), 1.18 (s, 3H), 1.06 (d, <i>J</i> = 3.8 Hz, 6H), 0.79 - 0.71 (m, 2H), 0.50 - 0.43 (m, 2H). LC/MS (ESI) (m/z): 573 [M+H] ⁺ .
Example 120	 (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(fluoromethyl)cyclopropyl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.30 (s, 1H), 8.89 (s, 1H), 7.75 (t, <i>J</i> = 53.0 Hz, 1H), 6.93 (s, 1H), 4.78 - 4.64 (m, 1H), 4.52 (d, <i>J</i> = 11.7 Hz, 1H), 4.34 - 4.22 (m, 3H), 4.21 - 4.14 (m, 1H), 3.27 - 3.22 (m, 2H), 3.13 - 3.00 (m, 1H), 1.35 - 1.20 (m, 6H), 0.93 - 0.82 (m, 4H), 0.81 - 0.75 (m, 2H), 0.64 - 0.55 (m, 2H). LC/MS (ESI) (m/z): 585 [M+H] ⁺ .

Example 121:

1-chloro-N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: 1,8-dichloro-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride

At 0°C, glacial acetic acid (0.2 mL) and water (0.2 mL) were added to the solution of 2-(6-(benzylthio)-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole (300 mg, 0.73 mmol) in dichloromethane (5 mL); then, sulfonyl chloride (379 mg, 2.81 mmol) was added dropwise slowly; and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with dichloromethane, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 330 mg, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 439 [M+H]⁺.

Step 2: 1,8-dichloro-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, triethylamine (207 mg, 2.27 mmol) and 1,8-dichloro-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride (330 mg, 0.73 mmol) were sequentially added to the solution of cyclopropylamine (80 mg, 1.20 mmol) in dichloromethane (8 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 180 mg, yield: 50.4%). LC/MS (ESI) (m/z): 458 [M+H]⁺.

Step 3: 1,8-dichloro-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, DIPEA (496 mg, 1.20 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (100 mg, 0.56 mmol) were added to the solution of 1,8-dichloro-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamid

e (180 mg, 0.40 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at 45°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 180 mg, yield: 77.8%). LC/MS (ESI) m/z: 588 [M+H]⁺.

Step

4:

1-chloro-N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (308 mg, 0.90 mmol), Ruphos (28 mg, 0.06 mmol) and Ruphos Pd G3 (28 mg, 0.03 mmol) were sequentially added to the solution of 1,8-dichloro-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methylimidazo[1,5-a]pyridine-6-sulfonamide (180 mg, 0.30 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (72 mg, 0.45 mmol) in 1,4-dioxane (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the title compound (yellow solid, 100 mg, yield: 45.4%). LC/MS (ESI) m/z: 708 [M+H]⁺.

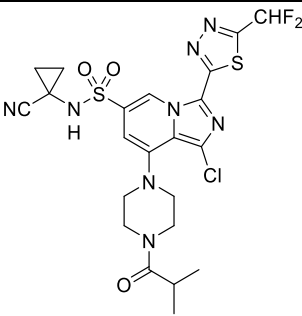
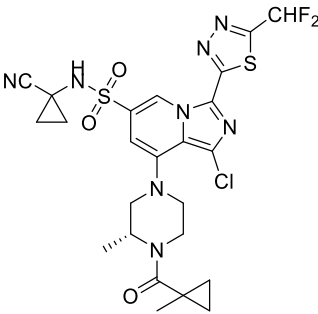
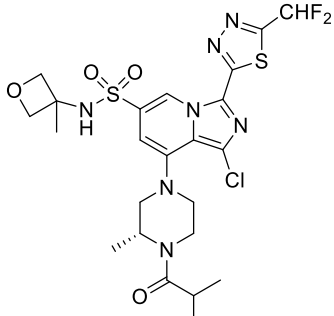
Step

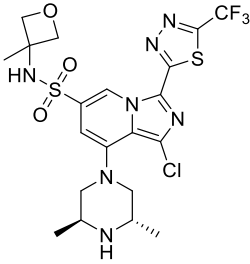
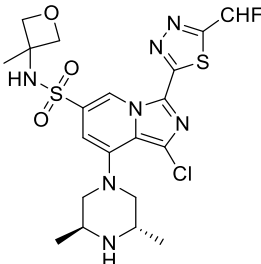
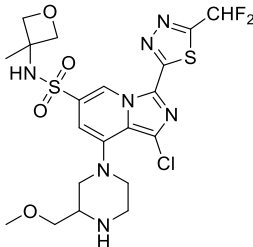
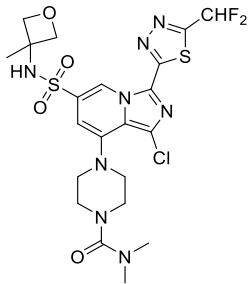
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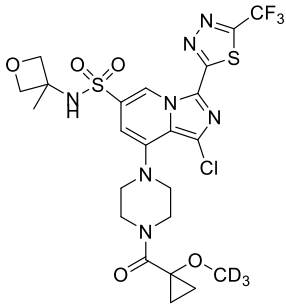
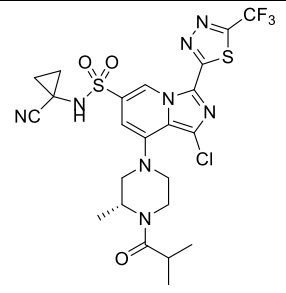
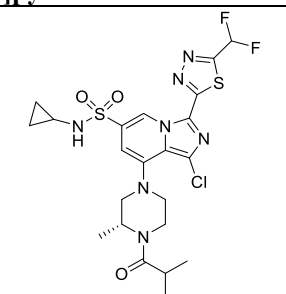
1-chloro-N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

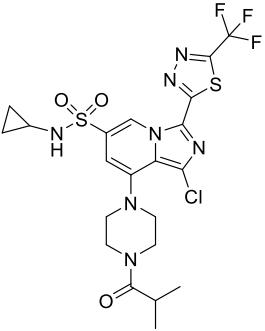
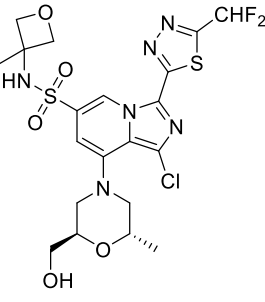
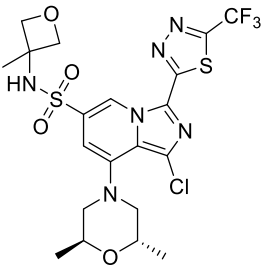
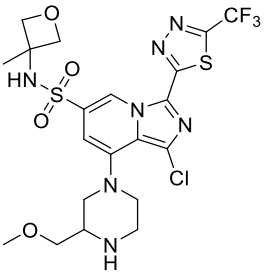
At 0°C, trifluoroacetic acid (1 mL) was dropwise added slowly to the solution of 1-chloro-N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methylimidazo[1,5-a]pyridine-6-sulfonamide (100 mg, 0.14 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 30 minutes. The mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 4 mg, yield: 23.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.59 (s, 1H), 8.28 (s, 1H), 8.13 (s, 1H), 6.73 (s, 1H), 3.84 - 3.71 (m, 4H), 3.44 - 3.34 (m, 4H), 2.99 - 2.91 (m, 1H), 2.30 - 2.22 (m, 1H), 1.05 (d, *J* = 6.3 Hz, 6H), 0.55 - 0.44 (m, 4H). LC/MS (ESI) (m/z): 578 [M+H]⁺.

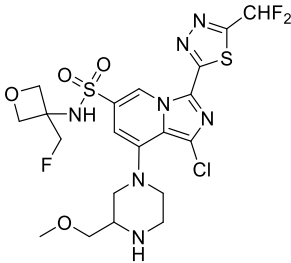
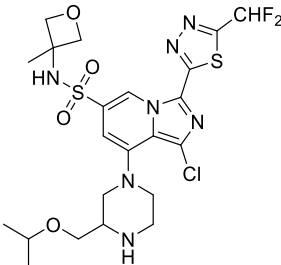
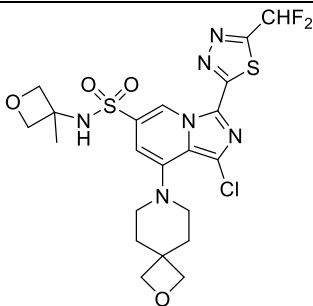
By referring to the preparation method in Example 121, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

Example	Structure and name	Analysis data
Example 122	 1-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.72 (s, 1H), 9.55 (s, 1H), 7.70 (t, <i>J</i> = 53.1 Hz, 1H), 6.84 (s, 1H), 3.85 - 3.80 (m, 4H), 3.18 - 3.05 (m, 4H), 2.98 - 2.92 (m, 1H), 1.52 - 1.47 (m, 2H), 1.41 - 1.37 (m, 2H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 585 [M+H] ⁺ .
Example 123	 (R)-1-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.72 (s, 1H), 9.56 (s, 1H), 7.70 (t, <i>J</i> = 52.6 Hz, 1H), 6.83 (s, 1H), 4.77 - 4.75 (m, 1H), 4.26 - 4.21 (m, 1H), 3.65 - 3.58 (m, 2H), 3.22 - 3.19 (m, 1H), 3.14 - 3.07 (m, 1H), 2.62 - 2.57 (m, 1H), 1.50 - 1.49 (m, 2H), 1.39 - 1.34 (m, 5H), 1.28 (s, 3H), 0.87 - 0.83 (m, 2H), 0.60 - 0.57 (m, 2H). LC/MS (ESI) (m/z): 611 [M+H] ⁺ .
Example 124	 (R)-1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.62 (s, 1H), 8.77 (s, 1H), 7.87 - 7.50 (m, 1H), 6.85 (s, 1H), 4.67 - 4.60 (m, 2H), 4.19 (d, <i>J</i> = 6.5 Hz, 2H), 3.60 (d, <i>J</i> = 12.8 Hz, 1H), 3.20 - 3.11 (m, 4H), 3.07 - 3.02 (m, 1H), 2.97 - 2.85 (m, 2H), 1.50 (s, 3H), 1.40 - 1.23 (m, 3H), 1.04 (d, <i>J</i> = 6.8 Hz, 6H). LC/MS (ESI) m/z: 604 [M+H] ⁺ .

Example 125	 1-chloro-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.21 (s, 1H), 6.86 (s, 1H), 4.63 (t, J = 5.5 Hz, 2H), 4.19 (d, J = 6.3 Hz, 2H), 3.58 - 3.44 (m, 4H), 2.77 - 2.53 (m, 2H), 1.50 (s, 3H), 1.18 (s, 6H). LC/MS (ESI) m/z: 566 $[\text{M}+\text{H}]^+$.
Example 126	 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, CD_3OD) δ 9.86 (s, 1H), 7.34 (t, J = 53.5 Hz, 1H), 6.88 (s, 1H), 4.81 - 4.77 (m, 2H), 4.32 (dd, J = 6.3, 2.0 Hz, 2H), 3.92 - 3.84 (m, 2H), 3.63 - 3.51 (m, 2H), 3.08 - 2.80 (m, 2H), 1.64 (s, 3H), 1.43 (d, J = 3.0 Hz, 6H). LC/MS (ESI) (m/z): 548 $[\text{M}+\text{H}]^+$.
Example 127	 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(methoxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, CD_3OD) δ 9.92 (s, 1H), 7.34 (t, J = 53.5 Hz, 1H), 6.93 (s, 1H), 4.80 - 4.78 (m, 2H), 4.37 - 4.32 (m, 2H), 3.91 - 3.85 (m, 1H), 3.76 - 3.65 (m, 4H), 3.59 - 3.52 (m, 2H), 3.47 (s, 3H), 3.16 - 3.07 (m, 2H), 1.66 (s, 3H). LC/MS (ESI) (m/z): 564 $[\text{M}+\text{H}]^+$.
Example 128	 4-(1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(3-methyloxetan-3-yl)sulfamoyl)imidazo[1,5-a]pyridin-2-yl)-N,N-dimethylpiperazine	^1H NMR (400 MHz, CD_3OD) δ 9.83 (s, 1H), 7.33 (t, J = 53.5 Hz, 1H), 6.85 (s, 1H), 4.79 (d, J = 6.3 Hz, 2H), 4.31 (d, J = 6.6 Hz, 2H), 3.57 - 3.52 (m, 4H), 3.24 - 3.18 (m, 4H), 2.91 (s, 6H), 1.63 (s, 3H). LC/MS (ESI) (m/z): 591 $[\text{M}+\text{H}]^+$.

	oyl)imidazo[1,5-a]pyridin-8-yl)-N,N-dimethylpiperazine-1-carboxamide	
Example 129	 1-chloro-8-(4-(1-(methoxy-d₃)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.79 (s, 1H), 6.92 (s, 1H), 4.64 (d, <i>J</i> = 6.2 Hz, 2H), 4.19 (d, <i>J</i> = 6.4 Hz, 2H), 4.10 - 3.69 (m, 4H), 3.23 - 3.11 (m, 4H), 1.50 (s, 3H), 1.05 - 1.00 (m, 2H), 0.95 - 0.91 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 639 [M+H]⁺.
Example 130	 (R)-1-chloro-N-(1-cyanocyclopropyl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.69 (s, 1H), 9.58 (s, 1H), 6.85 (s, 1H), 4.86 - 4.44 (m, 1H), 4.06 - 3.54 (m, 3H), 3.22 - 3.20 (m, 1H), 3.08 - 2.86 (m, 2H), 2.69 - 2.55 (m, 1H), 1.52 - 1.48 (m, 2H), 1.41 - 1.38 (m, 2H), 1.34 - 1.19 (m, 3H), 1.02 (d, <i>J</i> = 6.6 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 617 [M+H]⁺.
Example 131	 (R)-1-chloro-N-cyclopropyl-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.65 (s, 1H), 8.32 (s, 1H), 7.76 (t, <i>J</i> = 53.7 Hz, 1H), 6.83 (s, 1H), 4.63 - 4.13 (m, 1H), 3.95 - 3.69 (m, 1H), 3.64 - 3.58 (m, 1H), 3.23 - 3.15 (m, 2H), 3.10 - 3.01 (m, 1H), 2.99 - 2.80 (m, 2H), 2.31 - 2.27 (m, 1H), 1.28 - 1.22 (m, 3H), 1.04 (d, <i>J</i> = 4.6 Hz, 6H), 0.56 - 0.48 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 574 [M+H]⁺.

Example 132	 1-chloro-N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.62 (s, 1H), 8.35 (s, 1H), 6.88 (s, 1H), 3.89 - 3.56 (m, 4H), 3.18 - 3.05 (m, 4H), 2.99 - 2.93 (m, 1H), 2.31 - 2.27 (m, 1H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H), 0.57 - 0.52 (m, 2H), 0.51 - 0.46 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 578 [M+H]⁺.
Example 133	 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.61 (d, 1H), 8.81 (s, 1H), 7.69 (t, <i>J</i> = 53.1 Hz, 1H), 6.86 (s, 1H), 4.76 - 4.71 (m, 1H), 4.65 - 4.61 (m, 2H), 4.27 - 4.22 (m, 1H), 4.21 - 4.18 (m, 2H), 4.05 - 4.00 (m, 1H), 3.67 - 3.61 (m, 2H), 3.30 - 3.26 (m, 2H), 2.93 - 2.85 (m, 1H), 2.66 - 2.60 (m, 1H), 1.50 (s, 3H), 1.23 (d, <i>J</i> = 6.3 Hz, 3H). LC/MS (ESI) (<i>m/z</i>): 565 [M+H]⁺.
Example 134	 1-chloro-8-((2S,6S)-2,6-dimethylmorpholino)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.82 (s, 1H), 6.87 (s, 1H), 4.67 - 4.61 (m, 2H), 4.33 - 4.25 (m, 2H), 4.22 - 4.16 (m, 2H), 3.30 - 3.23 (m, 2H), 2.73 - 2.66 (m, 2H), 1.50 (s, 3H), 1.26 (d, <i>J</i> = 4.1 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 567 [M+H]⁺.
Example 135		¹H NMR (400 MHz, CD₃OD) δ 9.89 (s, 1H), 6.97 (s, 1H), 4.87 - 4.79 (m, 2H), 4.34 (d, <i>J</i> = 6.7 Hz, 2H), 3.92 - 3.83 (m, 1H), 3.75 - 3.64 (m, 4H), 3.60 - 3.53 (m, 2H), 3.47 (s, 3H), 3.20 - 3.09 (m, 2H),

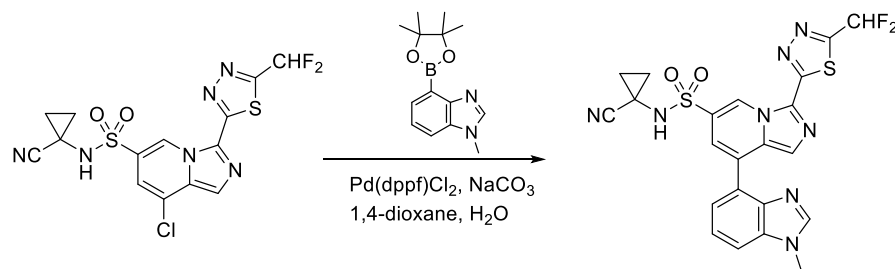
	1-chloro-8-(3-(methoxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	1.66 (s, 3H). LC/MS (ESI) (m/z): 582 [M+H] ⁺ .
Example 136	 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(3-(methoxymethyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.85 (s, 1H), 4.71 (s, 1H), 4.65 - 4.62 (m, 2H), 4.59 (s, 1H), 4.38 (d, <i>J</i> = 6.9 Hz, 2H), 3.64 - 3.41 (m, 3H), 3.28 (s, 3H), 3.19 - 3.15 (m, 3H), 3.07 - 3.02 (m, 2H), 2.76 - 2.71 (m, 1H). LC/MS (ESI) (m/z): 582 [M+H] ⁺ .
Example 137	 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(isopropoxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.90 (s, 1H), 7.34 (t, <i>J</i> = 53.4 Hz, 1H), 6.93 (s, 1H), 4.80 - 4.78 (m, 2H), 4.36 - 4.32 (m, 2H), 3.91 - 3.80 (m, 2H), 3.75 - 3.66 (m, 4H), 3.60 - 3.52 (m, 2H), 3.23 - 3.10 (m, 2H), 1.65 (s, 3H), 1.24 (d, <i>J</i> = 5.9 Hz, 6H). LC/MS (ESI) (m/z): 592 [M+H] ⁺ .
Example 138	 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 7.74 (d, <i>J</i> = 53.2 Hz, 1H), 6.82 (s, 1H), 4.63 (d, <i>J</i> = 6.2 Hz, 2H), 4.42 - 4.40 (m, 4H), 4.18 (d, <i>J</i> = 6.4 Hz, 2H), 3.37 - 3.36 (m, 4H), 2.08 - 2.06 (m, 2H), 1.49 (s, 3H), 1.25 - 1.23 (m, 2H). LC/MS (ESI) (m/z): 561 [M+H] ⁺ .

Example

139:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(1-methyl-1H-benzo[d]imidazol-

4-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

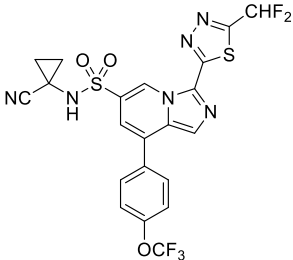
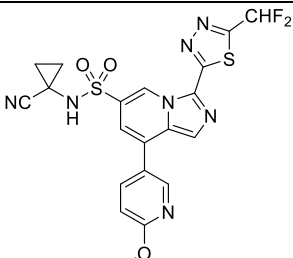
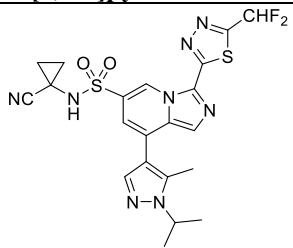
1:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(1-methyl-1H-benzo[d]imidazol-4-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, sodium carbonate (19 mg, 0.18 mmol) and Pd(dppf)Cl₂ (5 mg, 0.01 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (30 mg, 0.07 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborocyclopent-2-yl)-1H-benzo[d]imidazole (36 mg, 0.14 mmol) in 1,4-dioxane (2 mL) and water (0.4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 85°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 3.0 mg, yield: 8.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.03 (s, 1H), 8.36 (s, 1H), 8.09 (s, 1H), 8.04 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.76 - 7.57 (m, 2H), 7.48 (d, *J* = 1.3 Hz, 1H), 3.94 (s, 3H), 1.55 - 1.49 (m, 2H), 1.48 - 1.42 (m, 2H). LC/MS (ESI) *m/z*: 527 [M+H]⁺.

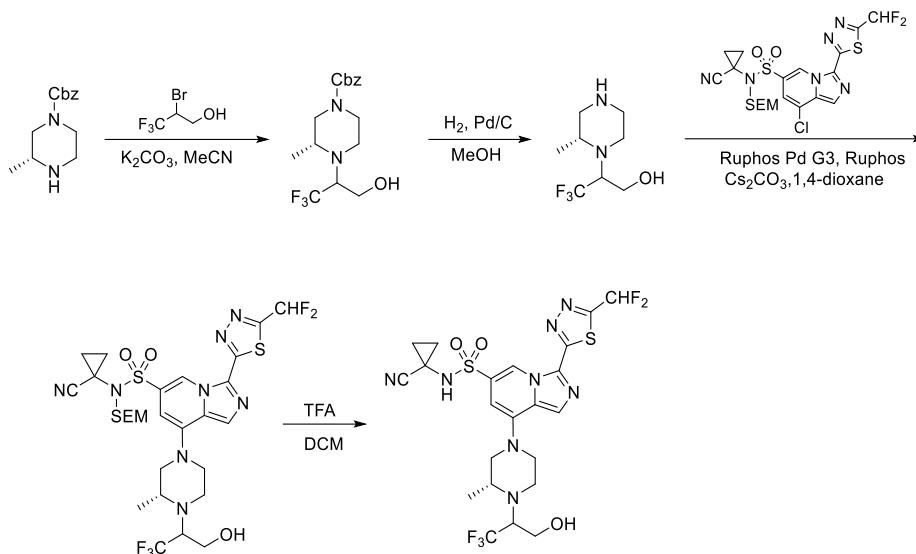
By referring to the preparation method in Example 139, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

Example	Structure and name	Analysis data
Example 140	N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2,3-dihydrobenzofuran-5-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (s, 1H), 9.60 (s, 1H), 8.05 (s, 1H), 7.74 (t, <i>J</i> = 28.3 Hz, 2H), 7.58 - 7.55 (m, 1H), 7.37 (d, <i>J</i> = 1.3 Hz, 1H), 7.01 (d, <i>J</i> = 8.3 Hz, 1H), 4.66 (t, <i>J</i> = 8.7 Hz, 2H), 3.32 - 3.29 (m, 2H), 1.53 - 1.49 (m, 2H), 1.43 - 1.39 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 515

	uran-5-yl)imidazo[1,5-a]pyridine-6-sulfonamide	[M+H] ⁺ .
Example 141	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(trifluoromethoxy)phenyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.03 (s, 1H), 8.06 (s, 1H), 7.95 (d, <i>J</i> = 8.6 Hz, 2H), 7.85 - 7.57 (m, 3H), 7.46 (s, 1H), 1.54 - 1.46 (m, 2H), 1.45 - 1.37 (m, 2H). LC/MS (ESI) <i>m/z</i> : 557 [M+H] ⁺ .
Example 142	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(6-methoxypyridin-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 8.63 (d, <i>J</i> = 2.5 Hz, 1H), 8.14 (dd, <i>J</i> = 8.6, 2.5 Hz, 1H), 8.06 (s, 1H), 7.70 (t, 1H), 7.43 (d, <i>J</i> = 1.0 Hz, 1H), 7.09 (d, <i>J</i> = 8.6 Hz, 1H), 3.97 (s, 3H), 1.47 - 1.43 (m, 2H), 1.37 - 1.34 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 504 [M+H] ⁺ .
Example 143	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(1-isopropyl-5-methyl-1H-pyrazol-4-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.94 (s, 1H), 9.68 (s, 1H), 7.99 (s, 1H), 7.92 (s, 1H), 7.70 (t, <i>J</i> = 53.2 Hz, 1H), 7.20 (s, 1H), 4.71 - 4.64 (m, 1H), 2.45 (s, 3H), 1.60 - 1.30 (m, 10H). LC/MS (ESI) (<i>m/z</i>): 519 [M+H] ⁺ .

Example 144:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R)-3-methyl-4-(1,1,1-trifluoro-3-hydroxypropan-2-yl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Benzyl (3R)-3-methyl-4-(1,1,1-trifluoro-3-hydroxypropan-2-yl)piperazine-1-carboxylate

At 0°C, 2-bromo-3,3,3-trifluoropropan-1-ol (200 mg, 1.0 mmol) and potassium carbonate (420 mg, 3.0 mmol) were added to the solution of (R)-3-methylpiperazine-1-benzyl carboxylate (240 mg, 1.0 mmol) in MeCN (5 mL); and the reaction mixture was stirred at 50°C for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (white solid, 120 mg, yield: 34.6%). LC/MS (ESI) (m/z): 347 [M+H]⁺.

Step 2: 3,3,3-trifluoro-2-((R)-2-methylpiperazin-1-yl)propan-1-ol

At room temperature, palladium on carbon (20 mg) with the mass fraction of 10% was added to the solution of (3R)-3-methyl-4-(1,1,1-trifluoro-3-hydroxypropan-2-yl)piperazine-1-benzyl carboxylate (120 mg, 0.35 mmol) in methanol (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 3 hours under an atmosphere of hydrogen at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (colorless oil, 60 mg, yield: 80.1%). LC/MS (ESI) (m/z): 213 [M+H]⁺.

Step

3:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R)-3-methyl-4-(1,1,1-trifluoro-3-hydroxypropan-2-yl)piperazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (117 mg, 0.36 mmol), Ruphos (6 mg, 0.015 mmol) and Ruphos Pd G3 (7 mg, 0.015 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methylimidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.12 mmol) and

(3,3,3-trifluoro-2-((R)-2-methylpiperazin-1-yl)propan-1-ol (23 mg, 0.18 mmol) in 1,4-dioxane (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 50 mg, yield: 56.8%). LC/MS (ESI) (m/z): 737 [M+H]⁺.

Step

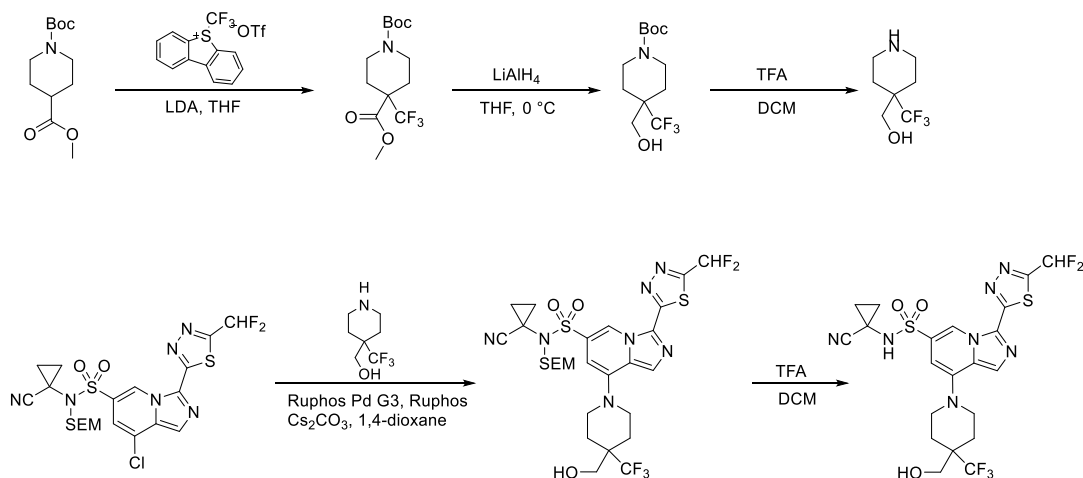
4:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R)-3-methyl-4-(1,1,1-trifluoro-3-hydroxypropan-2-yl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, TFA (1 mL) was added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R)-3-methyl-4-(1,1,1-trifluoro-3-hydroxypropan-2-yl)piperazin-1-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.067 mmol) in DCM (2 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 9 mg, yield: 21.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (s, 1H), 8.01 (s, 1H), 7.75 (d, *J* = 53.2 Hz, 1H), 6.66 (s, 1H), 6.32 - 6.12 (m, 1H), 4.23 - 4.14 (m, 1H), 3.59 - 3.57 (m, 1H), 3.10 - 3.04 (m, 3H), 2.88 - 2.81 (m, 3H), 2.74 - 2.64 (m, 2H), 1.50 - 1.45 (m, 2H), 1.41 - 1.36 (m, 2H), 1.16 - 1.12 (m, 3H). LC/MS (ESI) (m/z): 607 [M+H]⁺.

Example 145:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(hydroxymethyl)-4-(trifluoromethyl)piperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: N-tert-butoxycarbonyl-4-(trifluoromethyl)piperidine-4-carboxylate

Under an atmosphere of nitrogen at -78°C, lithium diisopropylamide (6.17 mL, 6.17 mmol, 1 M in THF) was dropwise added slowly to the solution of 1-tert-butoxycarbonyl-4-methyl piperidate (1 g, 4.11 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred at -78°C for 45 minutes; then, S-(trifluoromethyl)dibenzothiophenetrifluoromethyl sulfonate (2.48 g, 6.17 mmol) was added to the reaction system; the reaction mixture was allowed to gradually warm up to room temperature under an atmosphere of nitrogen, and then stirred for 16 hours. After completion of the reaction, aqueous ammonium chloride solution was added for quenching; the resulting mixture was extracted with ethyl acetate; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (yellow oil, 150 mg, yield: 11.7 %). ¹H NMR (400 MHz, CDCl₃) δ 4.24 - 4.01 (m, 2H), 3.83 (s, 3H), 2.83 - 2.62 (m, 2H), 2.31 - 2.27 (m, 2H), 1.77 - 1.70 (m, 2H), 1.45 (s, 9H).

Step 2: Tert-butyl 4-(hydroxymethyl)-4-(trifluoromethyl)piperidine-1-carboxylate

Under an atmosphere of nitrogen at 0°C, lithium aluminum hydride (37 mg, 0.96 mmol) was added to the solution of N-tert-butoxycarbonyl-4-trifluoromethylpiperidin-4-methyl formate (150 mg, 0.48 mmol) in tetrahydrofuran (3 mL). The reaction mixture was stirred at room temperature for 1 hour. After completion of the reaction, sodium sulfate decahydrate was added at 0°C; the mixture was stirred for 10 minutes, and filtered; and the filtrate was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow oil, 130 mg, yield: 95.2 %). LC/MS (ESI) m/z: 284 [M+H]⁺.

Step 3: (4-(trifluoromethyl)piperidin-4-yl) methanol, 2,2,2-trifluoroacetate

At 0°C, trifluoroacetic acid (0.2 mL) was added to the solution of 4-(hydroxymethyl)-4-(trifluoromethyl)piperidin-1-tert-butyl formate (130 mg, 0.46 mmol) in dichloromethane (1.5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (yellow oil, 100 mg, yield: 73.5 %). LC/MS (ESI) m/z: 184 [M+H]⁺.

Step

4:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(hydroxymethyl)-4-(trifluoromethyl)piperidin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (191.6 mg, 0.6 mmol), Ruphos (18.3 mg, 0.04 mmol) and Ruphos Pd G3 (32.8 mg, 0.04 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (110 mg, 0.2 mmol) and (4-(trifluoromethyl)piperidin-4-yl) methanol (71.8 mg, 0.4 mmol) in 1,4-dioxane (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 85°C for 3 hours under an atmosphere of nitrogen. After completion of

the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 90 mg, yield: 64.9%). LC/MS (ESI) (m/z): 708 [M+H]⁺.

Step

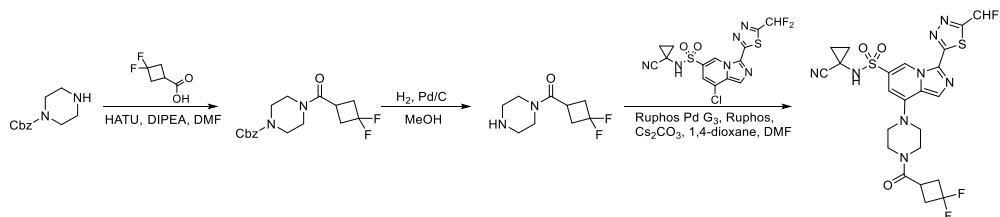
5:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(hydroxymethyl)-4-(trifluoromethyl)piperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (0.5 mL) was dropwise added to the solution of (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-pivaloylpiperazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (90 mg, 0.13 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure; and the residue was separated by pre-HPLC (C18, 10-50% acetonitrile in water containing 0.1% formic acid) to obtain the title compound (yellow solid, 28.3 mg, yield: 38.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.65 (s, 1H), 9.45 (s, 1H), 8.07 (s, 1H), 7.68 (t, *J* = 52.9 Hz, 1H), 6.66 (s, 1H), 5.13 (s, 1H), 3.74 (d, *J* = 4.3 Hz, 2H), 3.61 (d, *J* = 12.6 Hz, 2H), 3.30 - 3.17 (m, 2H), 2.10 - 1.97 (m, 2H), 1.99 - 1.82 (m, 2H), 1.60 - 1.43 (m, 2H), 1.46 - 1.32 (m, 2H). LC/MS (ESI) (m/z): 578 [M+H]⁺.

Example 146:

N-(1-cyanocyclopropyl)-8-(4-(3,3-difluorocyclobutane-1-carbonyl)piperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Benzyl 4-(3,3-difluorocyclobutane-1-carbonyl)piperazine-1-carboxylate

At room temperature, 3,3-difluorocyclobutan-1-carboxylic acid (204 mg, 1.50 mmol), N,N-diisopropylethylamine (439 mg, 3.41 mmol) and 2-(7-azabenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (569 mg, 1.50 mmol) was slowly added to the solution of piperazin-1-benzyl carboxylate (300 mg, 1.36 mmol) in N,N-dimethylformamide (4.5 mL). The mixture was stirred at room temperature for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate twice. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue

was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (colorless oil, 450 mg, yield: 97.7%). LC/MS (ESI) (m/z): 338 [M+H]⁺.

Step 2: (3,3-difluorocyclobutyl)(piperazin-1-yl)methanone

Under an atmosphere of nitrogen, palladium on carbon (100 mg) with the mass fraction of 10% was added to the solution of 4-(3,3-difluorocyclobutan-1-carbonyl)piperazin-1-benzyl formate (450 mg, 1.33 mmol) in methanol (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 1 hours under an atmosphere of hydrogen at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (colorless oil, 250 mg, yield: 92.0%). LC/MS (ESI) (m/z): 204 [M+H]⁺.

Step

3:

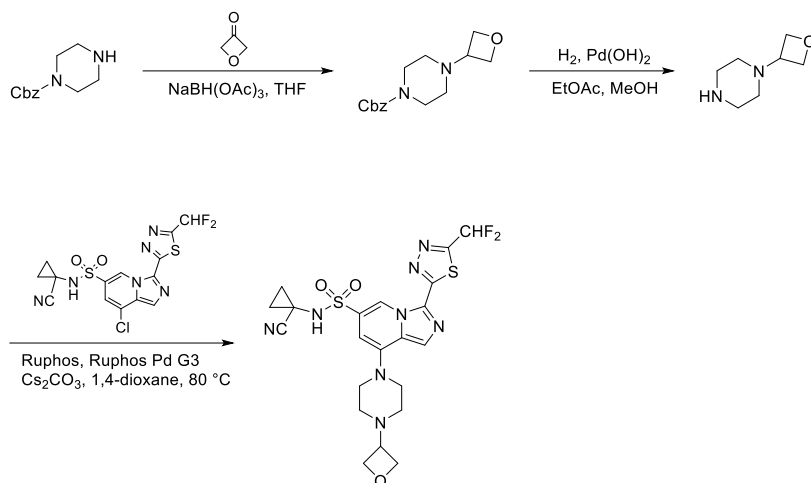
N-(1-cyanocyclopropyl)-8-(4-(3,3-difluorocyclobutane-1-carbonyl)piperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Under a protective atmosphere of nitrogen, cesium carbonate (181.5 mg, 0.56 mmol), Ruphos (17 mg, 0.037 mmol) and Ruphos Pd G3 (30 mg, 0.037 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-difluoromethyl)-1,3,4-thiadiazol-2-ylimidazo[1,5-a]pyridin-6-sulfonamide (80 mg, 0.19 mmol) and (3,3-difluorocyclobutyl)piperazin-1-ketone (76 mg, 0.37 mmol) in 1,4-dioxane (5 mL) and N,N-dimethylformamide (1.5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 10 minutes under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure; and the residue was separated by pre-HPLC (C18, 10-50% acetonitrile in H₂O and 0.1% formic acid) to obtain the title compound (yellow solid, 13.7 mg, yield: 12.3%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.69 (s, 1H), 9.49 (s, 1H), 8.10 (s, 1H), 7.69 (t, *J* = 53.2 Hz, 1H), 6.68 (s, 1H), 3.78 - 3.74 (m, 2H), 3.69 - 3.64 (m, 2H), 3.36 - 3.33 (m, 5H), 2.88 - 2.79 (m, 4H), 1.51 - 1.46 (m, 2H), 1.41 - 1.36 (m, 2H). LC/MS (ESI) (m/z): 599 [M+H]⁺.

Example

147:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(oxetan-3-yl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Benzyl 4-(oxetan-3-yl)piperazine-1-carboxylate

Under an atmosphere of nitrogen at room temperature, 3-oxacyclobutanone (380 mg, 5.45 mmol) and acetic acid sodium borohydride (1.92 g, 9.08 mmol) were added to the solution of benzyl-1-piperazine carbonate (1 g, 4.54 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred at room temperature for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was poured into ice water, and extracted with ethyl acetate; and the organic phase was washed with saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-80% ethyl acetate) to obtain the title compound (yellow oil, 510 mg, yield: 40.6%). LC/MS (ESI) m/z : 277 $[M+H]^+$.

Step 2: 1-(oxetan-3-yl)piperazine

At 0°C, palladium hydroxide on carbon (50 mg, 10% wt) was added to benzyl 4-(oxacyclobutan-3-yl)piperazine-1-carboxylate (500 mg, 1.81 mmol) in the mixed solution of ethyl acetate (5 mL) and methanol (2.5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 3 hours under an atmosphere of hydrogen at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (yellow solid, 250 mg, yield: 97.1 %). LC/MS (ESI) m/z : 143 $[M+H]^+$.

Step

3:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(oxetan-3-yl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

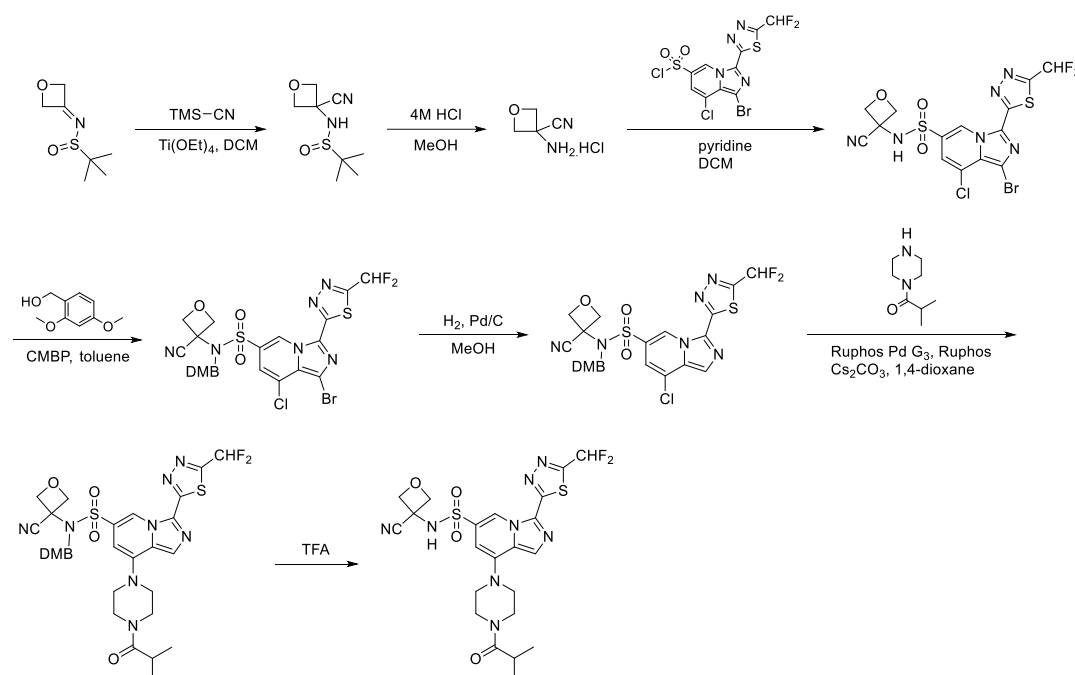
Under an atmosphere of nitrogen at room temperature, cesium carbonate (159 mg, 0.49 mmol), Ruphos (15 mg, 0.03 mmol) and Ruphos Pd G3 (14 mg, 0.02 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (70 mg, 0.16 mmol) and 1-(oxacyclobutan-3-yl)piperazine (23 mg, 0.16 mmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred at 80°C for 3 hours under an atmosphere of nitrogen. After completion

of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-70% ethyl acetate) and pre-HPLC to obtain the title compound (yellow solid, 5 mg, yield: 5.7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.02 (s, 1H), 7.68 (t, *J* = 53.1 Hz, 1H), 6.67 (s, 1H), 4.60 (t, *J* = 6.4 Hz, 2H), 4.52 (t, *J* = 6.0 Hz, 2H), 3.57 - 3.56 (m, 1H), 3.36 - 3.30 (m, 4H), 2.58 - 2.52 (m, 4H), 1.49 - 1.43 (m, 2H), 1.42 - 1.36 (m, 2H). LC/MS (ESI) (*m/z*): 537 [M+H]⁺.

Example

148:

N-(3-cyanooxetan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: N-(3-cyanooxetan-3-yl)-2-methylpropane-2-sulfonamide

Tetraethyl titanate (1.3 g, 5.7 mmol) was added to the solution of 2-methyl-N-(oxacyclobutan-3-ylidene)propan-2-sulfenamide (1 g, 5.7 mmol) in dichloromethane (20 mL). After adding, the reaction mixture was stirred for 10 minutes. Trimethylsilyl cyanide (1.5 mL, 11.4 mmol) was continued to be added to the above reaction mixture. The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was poured into saturated brine and filtered; the filtrate was extracted with dichloromethane three times; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-4% methanol) to obtain the title compound (yellow liquid, 900 mg, yield: 78.3%). LC/MS (ESI) (*m/z*): 203 [M+H]⁺.

Step 2: 3-aminooxetane-3-carbonitrile hydrochloride

At 0°C, the solution of 4M dioxane hydrochloride (1.5 mL, 6 mmol) was dropwise added slowly to the solution of N-(3-cyanooxacyclobutan-3-yl)-2-methylpropan-2-sulfenamide (400 mg, 2.0 mmol) in methanol (3 mL). The reaction mixture was stirred at 0°C for 30 minutes under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (white solid, 266 mg, yield: 100%), which was directly used in the next step without purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.90 (d, *J* = 8.0 Hz, 2H), 4.85 (d, *J* = 7.8 Hz, 2H).

Step 3: 1-bromo-8-chloro-N-(3-cyanooxetan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride (400 mg, 0.86 mmol) was added portionwise to the solution of 3-aminooxacyclobutan-3-formonitrile hydrochloride (232 mg, 1.72 mmol) in pyridine (2 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was acidified to pH=5 with 1N hydrochloric acid, and diluted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 280 mg, yield: 61.8%). LC/MS (ESI) (*m/z*): 525 [M+H]⁺.

Step 4: 1-bromo-8-chloro-N-(3-cyanooxetan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3,4-dimethylbenzyl)imidazo[1,5-a]pyridine-6-sulfonamide

2,4-dimethoxybenzyl alcohol (64 mg, 0.38 mmol) and cyanomethylenetri-*n*-butyl phosphine (138 mg, 0.57 mmol) were added to the solution of 1-bromo-8-chloro-N-(3-cyanooxacyclobutan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (100 mg, 0.19 mmol) in toluene (2 mL). The reaction mixture was stirred at 100°C for 6 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the title compound (yellow solid, 70 mg, yield: 54.5%). LC/MS (ESI) (*m/z*): 675 [M+H]⁺.

Step 5: 8-chloro-N-(3-cyanooxetan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3,4-dimethylbenzyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, 10% palladium on carbon (35 mg) was added to the solution of 1-bromo-8-chloro-N-(3-cyanooxacyclobutan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2,4-dimethoxybenzyl)imidazo[1,5-a]pyridin-6-sulfonamide (70 mg, 0.10 mmol) in ethanol (2 mL); the flask was

replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 6 hours under an atmosphere of hydrogen. After completion of the reaction, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the title compound (yellow solid, 30 mg, yield: 61.8%). LC/MS (ESI) (m/z): 597 [M+H]⁺.

Step

6:

N-(3-cyanooxetan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3,4-dimethylbenzyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, cesium carbonate (33 mg, 0.10 mmol), Ruphos (5 mg, 0.01 mmol) and Ruphos Pd G3 (4 mg, 0.005 mmol) were added to the solution of 8-chloro-N-(3-cyanooxacyclobutan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2,4-dimethoxybenzyl)imidazo[1,5-a]pyridine-6-sulfonamide (30 mg, 0.05 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (16 mg, 0.10 mmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred at 90°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature; water was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-70% ethyl acetate) to obtain the title compound (yellow solid, 22 mg, yield: 61.4%). LC/MS (ESI) m/z: 717 [M+H]⁺.

Step

7:

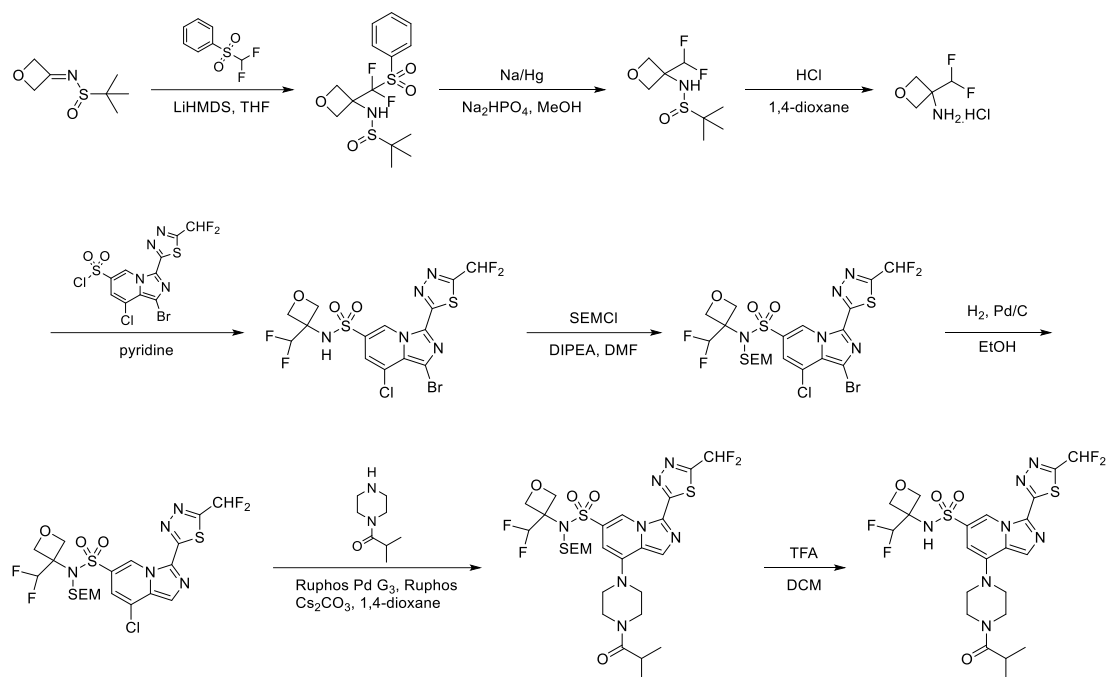
N-(3-cyanooxetan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (1 mL) was dropwise added slowly to the reaction flask containing N-(3-cyanooxacyclobutan-3-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2,4-dimethoxybenzyl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide (22 mg, 0.03 mmol). The reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 2 mg, yield: 11.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 1H), 8.10 (s, 1H), 7.86 - 7.47 (m, 1H), 6.66 (s, 1H), 4.87 (d, *J* = 7.4 Hz, 2H), 4.77 (d, *J* = 7.3 Hz, 2H), 3.80 - 3.69 (m, 4H), 3.40 - 3.35 (m, 4H), 2.98 - 2.90 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 567 [M+H]⁺.

Example

149:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: N-(3-(difluoro(phenylsulfonyl)methyl)oxetan-3-yl)-2-methylpropane-2-sulfinamide

Under an atmosphere of nitrogen at -78°C , lithium bis(trimethylsilyl)amide (11.4 mL, 11.4 mmol, 1M) was dropwise added slowly to the solution of 2-methyl-N-(oxacyclobutan-3-ylidene)propan-2-sulfenamide (1 g, 5.7 mmol) and ((difluoromethyl)sulfonyl)benzene (1.1 g, 5.7 mmol) in tetrahydrofuran (20 mL). After addition, the reaction mixture was warmed up from -78°C to room temperature, and stirred for 3 hours. After completion of the reaction, the reaction mixture was quenched with ice water, and extracted with ethyl acetate three times. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow liquid, 1.4 g, yield: 66.8%). LC/MS (ESI) (m/z): 368 $[\text{M}+\text{H}]^{+}$.

Step 2: N-(3-(difluoromethyl)oxetan-3-yl)-2-methylpropane-2-sulfinamide

At room temperature, disodium hydrogen phosphate (5.4 g, 38 mmol) and 20% sodium amalgam (1.1 g, 9.5 mmol) were added to the solution of N-(3-(difluoro(benzenesulfonyl)methyl)oxacyclobutan-3-yl)-2-methylpropan-2-sulfenamide (1.4 g, 3.81 mmol) in methanol (20 mL). The reaction mixture was stirred for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-40% ethyl acetate) to obtain the title compound (yellow liquid, 690 mg, yield: 79.7%). LC/MS (ESI) (m/z): 228 $[\text{M}+\text{H}]^{+}$.

Step 3: 3-(difluoromethyl)oxetan-3-amine hydrochloride

At 0°C , the solution of 4M dioxane hydrochloride (0.8 mL, 3.2 mmol) was dropwise added slowly to the

solution of N-(3-(difluoromethyl)oxacyclobutan-3-yl)-2-methylpropan-2-sulfenamide (400 mg, 1.76 mmol) in methanol (3.5 mL). The reaction mixture was stirred at 0°C for 30 minutes under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (white solid, 281 mg, yield: 100%), which was directly used in the next step of reaction without purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.60 (t, *J* = 54.2 Hz, 1H), 4.73 (d, *J* = 8.1 Hz, 2H), 4.67 (d, *J* = 8.0 Hz, 2H).

Step

4:

1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride (300 mg, 0.65 mmol) was added portionwise to the solution of 3-(difluoromethyl)oxacyclobutan-3-amine hydrochloride (206 mg, 1.29 mmol) in pyridine (5 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was acidified to pH-5 with 1N hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow solid, 120 mg, yield: 33.7%). LC/MS (ESI) (*m/z*): 550 [M+H]⁺.

Step

5:

1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxetan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, N, N-diisopropylethylamine (84 mg, 0.64 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (73 mg, 0.44 mmol) were added to the solution of 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxacyclobutan-3-yl)imidazo[1,5-a]pyridin-6-sulfonamide (120 mg, 0.22 mmol) in DMF (2 mL). The reaction mixture was stirred at 0°C for 0.5 hour under an atmosphere of nitrogen. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 100 mg, yield: 67.4%). LC/MS (ESI) *m/z*: 680 [M+H]⁺.

Step

6:

8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxetan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, 10% palladium on carbon (10 mg) was added to the solution of 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (100 mg, 0.15mmol) in ethanol

(10 mL); the flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 6 hours under an atmosphere of hydrogen. After completion of the reaction, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 70 mg, yield: 79.2%). LC/MS (ESI) (m/z): 602 [M+H]⁺.

Step

7:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, cesium carbonate (76 mg, 0.23 mmol), Ruphos (11 mg, 0.02 mmol) and Ruphos Pd G3 (10 mg, 0.01 mmol) were added to the solution of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (70 mg, 0.12 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (36 mg, 0.23 mmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred at 90°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 60 mg, yield: 71.5%). LC/MS (ESI) m/z: 722 [M+H]⁺.

Step

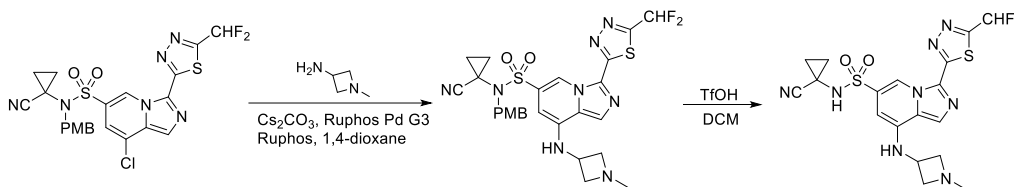
8:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (1 mL) was dropwise added slowly to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(difluoromethyl)oxacyclobutan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (60 mg, 0.08 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 21 mg, yield: 42.7%). ¹H NMR (400 MHz, CD₃OD) δ 9.86 (s, 1H), 7.95 (s, 1H), 7.33 (t, *J* = 53.5 Hz, 1H), 6.78 (d, *J* = 1.2 Hz, 1H), 6.23 (t, *J* = 55.6 Hz, 1H), 4.83 - 4.75 (m, 2H), 4.73 - 4.64 (m, 2H), 3.94 - 3.84 (m, 4H), 3.50 - 3.34 (m, 4H), 3.09 - 2.95 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 592 [M+H]⁺.

Example 150:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1-methylazetidin-3-yl)amino)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-8-((1-methylazetidin-3-yl)amino)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, cesium carbonate (45 mg, 0.14 mmol), Ruphos (4 mg, 0.09 mmol) and Ruphos Pd G3 (4 mg, 0.05 mmol) were sequentially added to the mixed solution of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(cyano)cyclopropyl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-6-sulfonamide (25 mg, 0.046 mmol) and 1-methylazetidin-3-amine (6 mg, 0.07 mmol) in 1,4-dioxane (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched, and extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 20 mg, yield: 74.1%). LC/MS (ESI) (m/z): 601 [M+H]⁺.

Step

2:

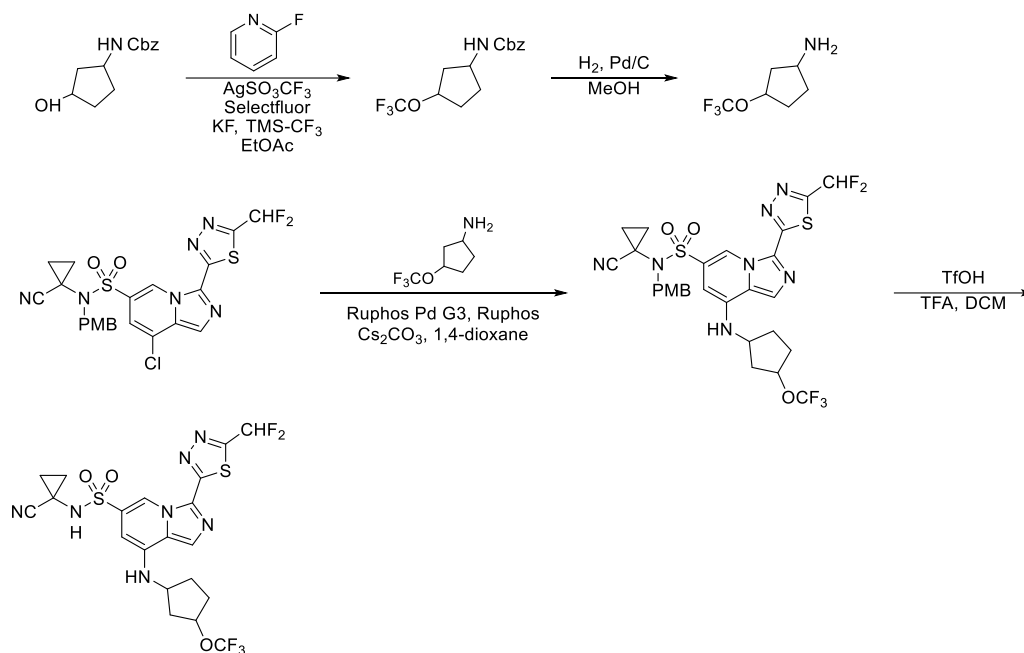
N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1-methylazetidin-3-yl)amino)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoromethanesulfonic acid (0.1 mL) was added to the solution of N-(1-(cyano)cyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-8-((1-methylazetidin-3-yl)amido)imidazo[1,5-a]pyridine-6-sulfonamide (20 mg, 0.03 mmol) in dichloromethane (2 mL); and the reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (white solid, 8 mg, yield: 50.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.43 (s, 1H), 8.12 (s, 1H), 7.81 - 7.55 (m, 2H), 6.07 (s, 1H), 4.49 - 4.42 (m, 1H), 4.33 - 4.25 (m, 2H), 3.85 - 3.74 (m, 2H), 2.76 (s, 3H), 1.49 - 1.45 (m, 2H), 1.41 - 1.37 (m, 2H). LC/MS (ESI) (m/z): 481 [M+H]⁺.

Example

151:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3-(trifluoromethoxy)cyclopentyl)amino)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Benzyl (3-(trifluoromethoxy)cyclopentyl)carbamate

Under an atmosphere of nitrogen at room temperature, silver trifluoromethanesulfonate (3.3 g, 12.8 mmol), 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (2.3 g, 6.4 mmol) and potassium fluoride were sequentially added to a sealed tube; and then, ethyl acetate (10 mL), 2-fluoropyridine (1.2 g, 12.8 mmol) and (trifluoromethyl)trimethylsilane (1.8 g, 12.8 mmol) were sequentially added. The reaction mixture was stirred in the sealed tube at room temperature for 16 hours. After completion of the reaction, the reaction mixture was filtered and concentrated under reduced pressure. The residue was separated by silica gel chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title compound (colorless liquid, 290 mg, yield: 22.5%).

Step 2: 3-(trifluoromethoxy)cyclopentan-1-amine

Under an atmosphere of nitrogen at room temperature, 10% palladium on carbon (50 mg) was added to the solution of (3-(trifluoromethoxy)cyclopentyl)aminobenzyl formate (290 mg, 0.96 mmol) in methanol (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for one hour under an atmosphere of hydrogen. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain a crude title compound (colorless liquid, 90 mg, yield: 55.6%), which was directly used in the next step of reaction without purification.

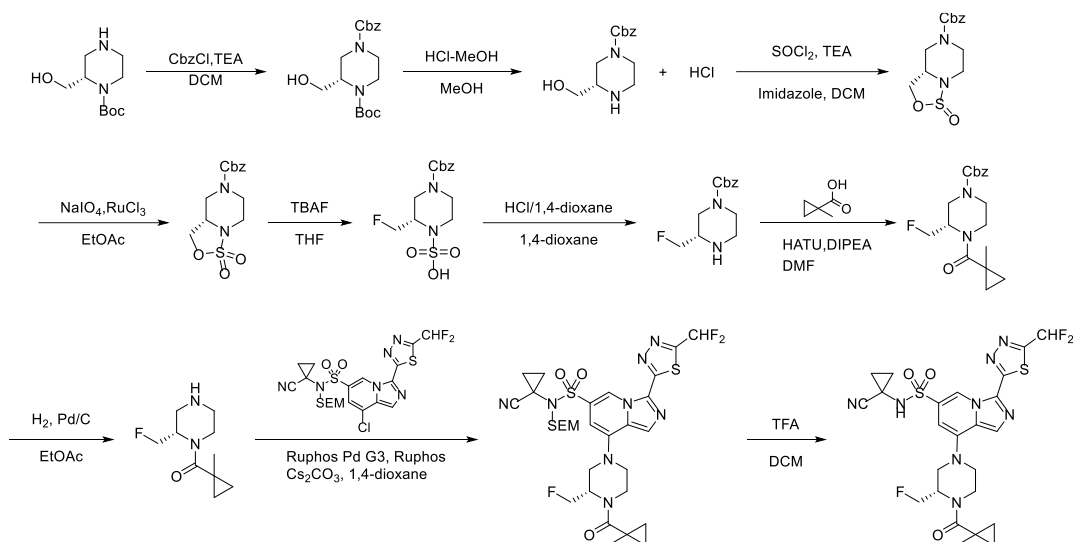
By referring to the preparation method in Example 135, Steps 3-4 were implemented according to a similar route by starting from appropriate starting materials to obtain the target compound.

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3-(trifluoromethoxy)cyclopentyl)amido)imidazo[1,5-a]pyridin-6-sulfonamide (yellow solid). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.41 (s, 1H), 9.37 (s, 1H), 8.21 (s, 1H), 7.82 - 7.54 (m, 1H), 7.21 (d, *J* = 6.6 Hz, 1H), 6.20 (s, 1H), 4.98 - 4.93 (m, 1H),

4.01 - 3.95 (m, 1H), 2.69 (d, $J = 7.5$ Hz, 1H), 2.24 - 2.16 (m, 1H), 2.03 (d, $J = 6.5$ Hz, 2H), 1.93 - 1.81 (m, 2H), 1.48 - 1.44 (m, 2H), 1.39 - 1.34 (m, 2H). LC/MS (ESI) (m/z): 564 $[M+H]^+$.

Example 152:

(S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(fluoromethyl)-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: 4-benzyl 1-(tert-butyl) (S)-2-(hydroxymethyl)piperazine-1,4-dicarboxylate

At 0°C, benzyl chloroformate (2.37 g, 13.8 mmol) and triethylamine (2.81 g, 27.7 mmol) were sequentially dropwise added to the solution of (S)-2-(hydroxymethyl)piperazine-1-tert-butyl carboxylate (2 g, 9.3 mmol) in dichloromethane (20 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (white solid, 3.1 g, yield: 95.67%). LC/MS (ESI) (m/z): 351 $[M+H]^+$.

Step 2: Benzyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate hydrochloride

At 0°C, hydrochloric acid/methanol (5 mL, 4 mol/L) was added to the solution of 1-(tert-butyl)(S)-2-(hydroxymethyl)piperazine-4-benzyl-1,4-dicarboxylate (1.0 g, 2.8 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for one hour. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain a crude title compound (white solid, 800 mg, yield: 100%), which was directly used in the next step of reaction. LC/MS (ESI) (m/z): 251 $[M+H]^+$.

Step 3: Benzyl (3aS)-tetrahydro-[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1-oxide

At 0°C, imidazole (8 mg, 0.6 mmol) was added to the solution of (S)-3-(hydroxymethyl)piperazine-1-benzyl carboxylate hydrochloride (800 mg, 2.8 mmol) in DCM (10 mL); and then, SOCl_2 (0.24 mL, 3.36 mmol) was dropwise added slowly. The reaction mixture was stirred at room temperature for 2 hours. After

completion of the reaction, 10 mL of ice water was added to the reaction mixture, and stirred at for 10 minutes. The organic phase and the aqueous phase were separated; and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow oil, 500 mg, yield: 60.3%). LC/MS (ESI) (m/z): 297 [M+H]⁺.

Step 4: Benzyl (S)-tetrahydro-[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1,1-dioxide

At 0°C, (3aS)-tetrahydro-[1,2,3]oxathiazolo[3,4-a]pyrazin-5(3H)-benzyl carboxylate-1-oxide (300 mg, 1.0 mmol) was dissolved in the solution of ethyl acetate (3 mL); acetonitrile (8 mL), water (8 mL) and ruthenium trichloride (5 mg, 0.02 mmol) were added; and then, sodium periodate (540 mg, 2.5 mmol) was added portionwise. The reaction mixture was stirred at 0°C for 2 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow oil, 270 mg, yield: 85.4%). LC/MS (ESI) (m/z): 313 [M+H]⁺.

Step 5: (S)-4-((benzyloxy)carbonyl)-2-(fluoromethyl)piperazine-1-sulfonic acid

At room temperature, tetrabutylammonium fluoride (360 mg, 2.2 mmol) was added to the solution of (S)-tetrahydro-[1,2,3]oxathiazolo[3,4-a]pyrazin-5(3H)-benzyl carboxylate 1,1-dioxide (270 mg, 0.87 mmol) in tetrahydrofuran (8 mL); and the reaction mixture was stirred at 65-70°C for 3 hours. The reaction mixture was concentrated under reduced pressure to obtain a crude title compound (yellow oil, 400 mg, yield: 100%), which was directly used in the next step of reaction.

Step 6: Benzyl (S)-3-(fluoromethyl)piperazine-1-carboxylate

At 0°C, hydrogen chloride /1,4-dioxane (4 mL, 4 mol/L) was added to the solution of (S)-4-((benzyloxy)carbonyl)-2-(fluoromethyl)piperazin-1-sulfonic acid (400 mg, 0.87 mmol) in 1,4-dioxane (5 mL); and the reaction mixture was stirred at room temperature for one hour. The reaction mixture was poured into ice water, and washed twice with methyltert-butyl ether. The aqueous phase was alkalized to pH 8-9 with 1N sodium hydroxide aqueous solution, and then extracted with dichloromethane twice. The organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow oil, 210 mg, yield: 95.8%). LC/MS (ESI) (m/z): 253 [M+H]⁺.

Step 7: Benzyl (S)-3-(fluoromethyl)-4-(1-methylcyclopropane-1-carbonyl)piperazine-1-carboxylate

At 0°C, 1-methylcyclopropan-1-carboxylic acid (107 mg, 1.07 mmol), N,N-diisopropylethylamine (416 mg, 2.6 mmol) and HATU (380 mg, 1.5 mmol) were added to the solution of (S)-3-(fluoromethyl)piperazin-1-benzyl carboxylate (210 mg, 0.83 mmol) in N,N- (5 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl

acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (white solid, 50 mg, yield: 18.0%). LC/MS (ESI) (m/z): 335 [M+H]⁺.

Step 8: (S)-(2-(fluoromethyl)piperazin-1-yl)(1-methylcyclopropyl)methanone

Under an atmosphere of nitrogen, palladium on carbon (10 mg) with the mass fraction of 10% was added to the solution of (S)-3-(fluoromethyl)-4-(1-methylcyclopropan-1-carbonyl)piperazin-1-benzyl carboxylate (50 mg, 0.15 mmol) in ethyl acetate (3 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 2 hours under an atmosphere of hydrogen at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (colorless oil, 25 mg, yield: 83.5%). LC/MS (ESI) (m/z): 201 [M+H]⁺.

Step 9:

(S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(fluoromethyl)-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (87 mg, 0.27 mmol), Ruphos (8 mg, 0.02 mmol) and Ruphos Pd G3 (8 mg, 0.01 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.09 mmol) and (S)-(2-(fluoromethyl)piperazin-1-yl)(1-methylcyclopropyl)ketone (25 mg, 0.13 mmol) in 1,4-dioxane (2 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 40 mg, yield: 61.9%). LC/MS (ESI) (m/z): 725 [M+H]⁺.

Step

10:

(S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(fluoromethyl)-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

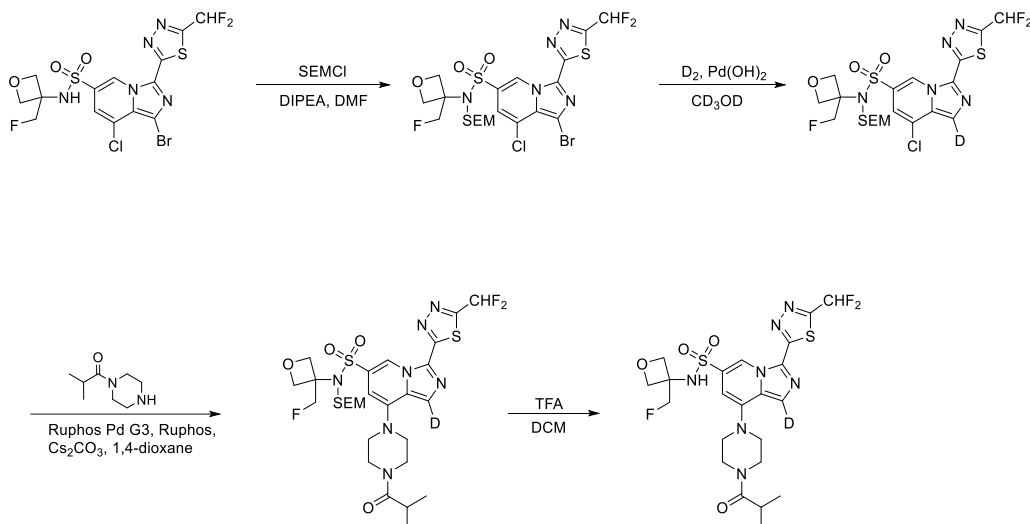
At 0°C, trifluoroacetic acid (0.5 mL) was added to the solution of (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(fluoromethyl)-4-(1-methylcyclopropan-1-carbonyl)piperazin-1-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (40 mg, 0.06 mmol) in dichloromethane (1 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 6.5 mg, yield: 19.8%). ¹H

NMR (400 MHz, DMSO-*d*₆) δ 9.71 (s, 1H), 9.49 (s, 1H), 7.98 (s, 1H), 7.82 - 7.55 (m, 1H), 6.74 (s, 1H), 4.91 - 4.78 (m, 2H), 4.36 - 4.27 (m, 1H), 3.87 - 3.81 (m, 1H), 3.75 - 3.70 (m, 1H), 3.35 - 3.32 (m, 1H), 3.14 - 3.00 (m, 3H), 1.52 - 1.48 (m, 2H), 1.41 - 1.37 (m, 2H), 1.30 (s, 3H), 0.93 - 0.87 (m, 2H), 0.67 - 0.58 (m, 2H). LC/MS (ESI) (m/z): 595 [M+H]⁺.

Example

153:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d



Step

1:

1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, N,N-diisopropylethylamine (105 mg, 0.81 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (67 mg, 0.40 mmol) were sequentially added to the solution of 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxacyclobutan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (145 mg, 0.27 mmol) in N,N-dimethylformamide (2 mL). The reaction mixture was stirred at room temperature for one hour. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was pulped with petroleum ether to obtain the title compound (yellow solid, 143 mg, yield: 79.4%). LC/MS (ESI) (m/z): 662 [M+H]⁺.

Step

2:

8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d

Under an atmosphere of nitrogen, palladium hydroxide on carbon (10 mg) with the mass fraction of 20% was added to the solution of

1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (65 mg, 0.62 mmol) in deuterio methanol (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 20 °C for one hour under an atmosphere of deuterium at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (yellow solid, 40 mg, yield: 69.6%). LC/MS (ESI) (m/z): 585 [M+H]⁺.

Step

3:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d

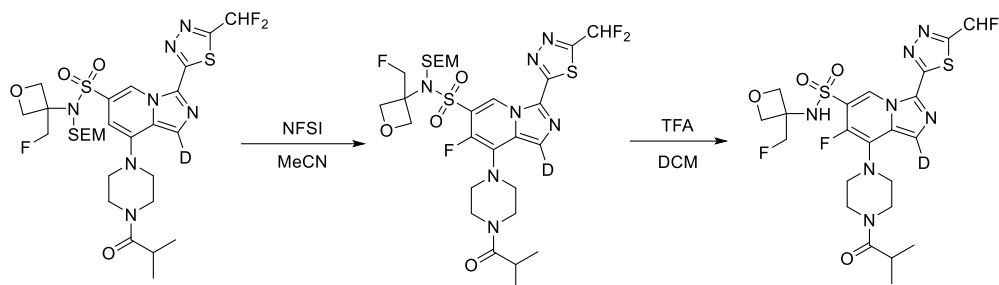
Under an atmosphere of nitrogen, cesium carbonate (44 mg, 0.13mmol), Ruphos (6 mg, 0.014 mmol), and Ruphos Pd G3 (11 mg, 0.014 mmol) were sequentially added to the solution of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide-1-deuterium (40 mg, 0.068 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (21 mg, 0.13 mmol) in 1,4-dioxane (2 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 30 minutes under an atmosphere of nitrogen. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-70% ethyl acetate) to obtain the title compound (yellow solid, 44 mg, yield: 91.6%). LC/MS (ESI) (m/z): 705 [M+H]⁺.

Step

4:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d

At 0°C, trifluoroacetic acid (0.2 mL) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxacyclobutan-3-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide-1-deuterium (15 mg, 0.02 mmol) in dichloromethane (0.6 mL). The reaction mixture was stirred at 0°C for one hour. After completion of the reaction, the reaction mixture was dropped to 5% aqueous sodium bicarbonate solution that was cooled with ice water, and extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by pre-HPLC (C18, 10-50% acetonitrile in H₂O and 0.1% formic acid) to obtain the title compound (yellow solid, 3 mg, yield: 24.5%). ¹H NMR (400 MHz, CD₃OD) δ 9.85 (s, 1H), 7.33 (t, *J* = 53.5 Hz, 1H), 6.78 (s, 1H), 4.82 - 4.79 (m, 2H), 4.78 (s, 1H), 4.66 (s, 1H), 4.47 (d, *J* = 7.1 Hz, 2H), 3.92 - 3.86 (m, 4H), 3.44 - 3.41 (m, 2H), 3.37 - 3.34 (m, 2H), 3.07 - 2.99 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 575 [M+H]⁺.

Example**154:****3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpi perazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d****Step****1:****3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpi perazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d**

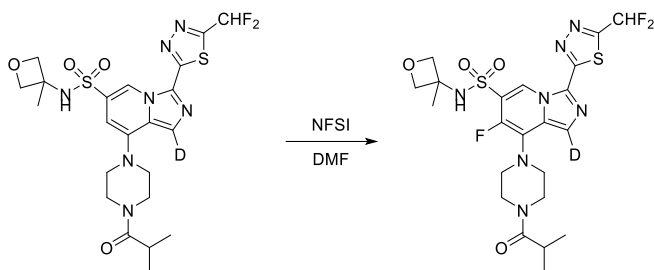
Under an atmosphere of nitrogen, N-fluorodibenzene sulfonamide (16 mg, 0.05 mmol) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxacyclobutan-3-yl)-8-(4-isobutyrylpi perazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide-1-deuterium (30 mg, 0.04 mmol) in acetonitrile (0.7 mL). The reaction mixture was stirred at room temperature for 1 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow solid, 12 mg, yield: 39.0%). LC/MS (ESI) (m/z): 605 [M+H]⁺.

Step**2:****3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-N-(3-(fluoromethyl)oxetan-3-yl)-8-(4-isobutyrylpi perazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d**

At 0°C, trifluoroacetic acid (0.2 mL) was dropwise added slowly to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-N-(3-(fluoromethyl)oxacyclobutan-3-yl)-8-(4-isobutyrylpi perazin-1-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide-1-deuterium (12 mg, 0.02 mmol) in dichloromethane (0.6 mL). The reaction mixture was stirred at room temperature for 0.5 hour. The reaction mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 1.1 mg, yield: 11.2%). ¹H NMR (400 MHz, CD₃OD) δ 9.89 (d, J = 5.4 Hz, 1H), 7.33 (t, J = 53.5 Hz, 1H), 4.85 - 4.82 (m, 2H), 4.79 (s, 1H), 4.67 (s, 1H), 4.51 - 4.46 (m, 2H), 3.89 - 3.77 (m, 4H), 3.50 - 3.41 (m, 4H), 3.07 - 2.98 (m, 1H), 1.16 (d, J = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 593 [M+H]⁺.

Example**155:**

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d



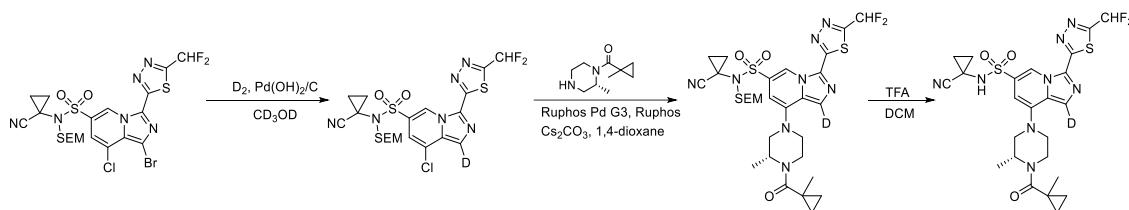
Step 1:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d

Under an atmosphere of nitrogen at room temperature, N-fluorodibenzene sulfonamide (5.7 mg, 0.018 mmol) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d (5 mg, 0.009 mmol) in N,N-dimethylformamide (0.5 mL). The reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was filtered; and the filtrate was purified by pre-HPLC to obtain the title compound (yellow solid, 2 mg, yield: 38.7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.65 (d, *J* = 5.3 Hz, 1H), 8.97 (s, 1H), 7.81 - 7.53 (m, 1H), 4.71 (d, *J* = 6.3 Hz, 2H), 4.23 (d, *J* = 6.4 Hz, 2H), 3.74 - 3.66 (m, 4H), 3.43 - 3.39 (m, 4H), 2.97 - 2.91 (m, 1H), 1.55 (s, 3H), 1.04 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (*m/z*): 575 [M+H]⁺.

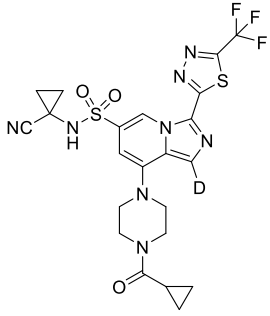
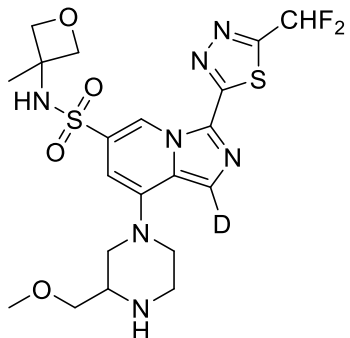
Example 156:

(R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d



By referring to the preparation method in Example 153, this example was implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 9.48 (s, 1H), 7.69 (t, *J* = 53.2 Hz, 1H), 6.68 (s, 1H), 4.76 - 4.63 (m, 1H), 4.27 (d, *J* = 13.4 Hz, 1H), 3.78 - 3.43 (m, 3H), 3.07 - 2.87 (m, 2H), 1.50 - 1.26 (m, 10H), 0.90 - 0.79 (m, 2H), 0.64 - 0.53 (m, 2H). LC/MS (ESI) (*m/z*): 578 [M+H]⁺.

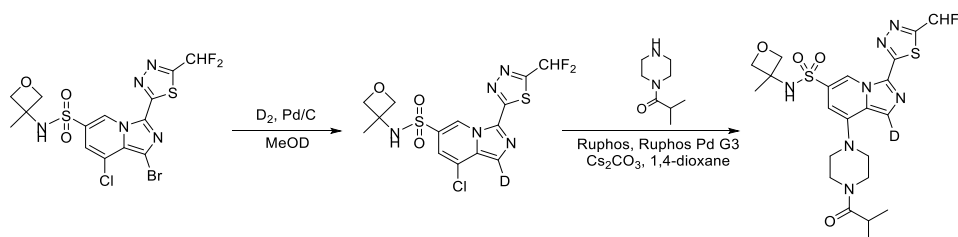
By referring to the preparation method in Example 156, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

Example	Structure and name	Analysis data
Example 157	 N-(1-cyanocyclopropyl)-8-(4-(cyclopropanecarbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.64 (s, 1H), 9.49 (s, 1H), 6.70 (s, 1H), 4.07 – 3.88 (m, 2H), 3.83 – 3.66 (m, 2H), 3.48 – 3.36 (m, 2H), 3.36 – 3.34 (m, 2H), 2.06 – 1.95 (m, 1H), 1.52 – 1.35 (m, 4H), 0.82 – 0.70 (m, 4H). LC/MS (ESI) (m/z): 568 [M+H] ⁺ .
Example 158	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(methoxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d	¹ H NMR (400 MHz, CD ₃ OD) δ 9.88 (s, 1H), 7.33 (t, <i>J</i> = 53.5 Hz, 1H), 6.82 (s, 1H), 4.78 - 4.76 (m, 2H), 4.33 (d, <i>J</i> = 6.7 Hz, 2H), 3.89 - 3.80 (m, 3H), 3.72 - 3.68 (m, 2H), 3.65 - 3.60 (m, 2H), 3.47 (s, 3H), 3.14 - 3.11 (m, 2H), 1.65 (s, 3H). LC/MS (ESI) (m/z): 531 [M+H] ⁺ .

Example

159:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d



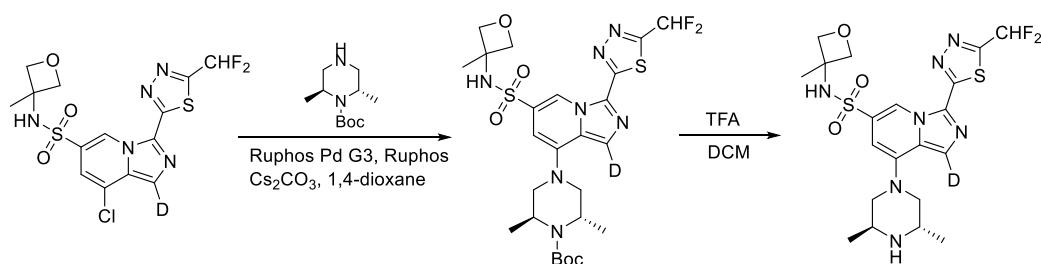
Step 1: Preparation of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d

Under an atmosphere of nitrogen, palladium on carbon (50 mg) with the mass fraction of 10% was added to the solution of 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxacyclobutan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (180 mg, 0.35 mmol) in deuterio methanol (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 6 hours under an atmosphere of deuterium at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (yellow solid, 120 mg, yield: 78.55%). LC/MS (ESI) m/z : 437/439 $[M+H]^+$.

Step 2: Preparation of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d

Under an atmosphere of nitrogen, cesium carbonate (112 mg, 0.344 mmol), Ruphos (11 mg, 0.024 mmol) and Ruphos Pd G3 (10 mg, 0.012 mmol) were sequentially added to the solution of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxacyclobutan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-deuterium (50 mg, 0.114 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (36 mg, 0.23 mmol) in 1,4-dioxane (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 18.2 mg, yield: 28.7%). ^1H NMR (400 MHz, DMSO- d_6) δ 9.61 - 9.57 (m, 1H), 8.72 (s, 1H), 7.83 - 7.53 (m, 1H), 6.70 (s, 1H), 4.63 (d, J = 6.2 Hz, 2H), 4.18 (d, J = 6.5 Hz, 2H), 3.84 - 3.70 (m, 4H), 3.39 - 3.34 (m, 4H), 2.99 - 2.91 (m, 1H), 1.50 (s, 3H), 1.05 (d, J = 6.7 Hz, 6H). LC/MS (ESI) m/z : 557 $[M+H]^+$.

Example 160: 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide-1-d

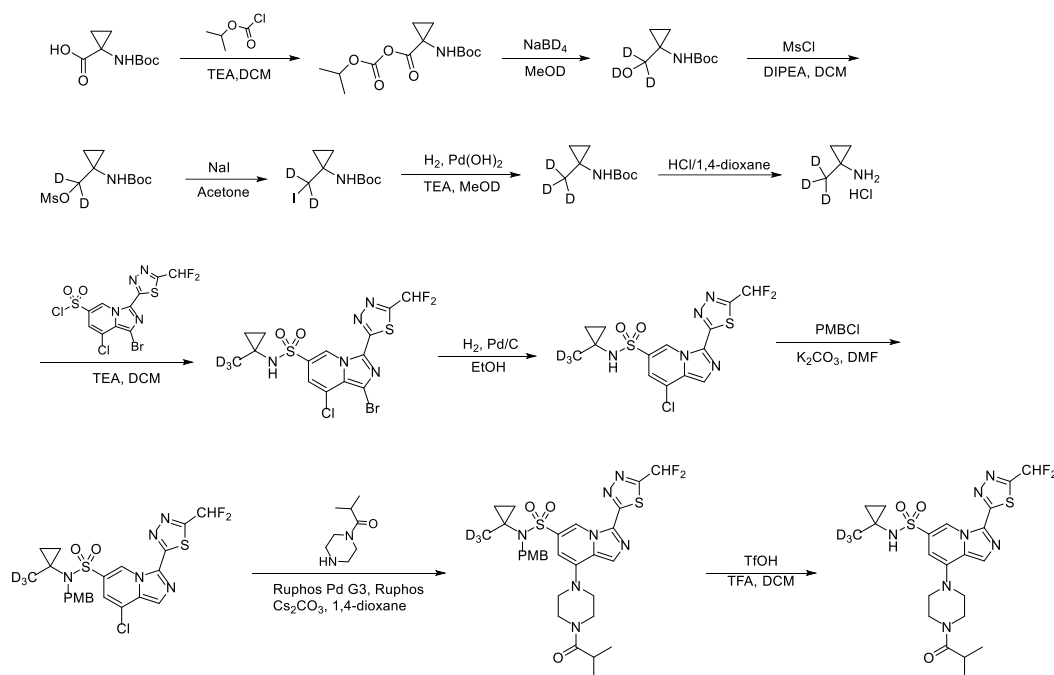


The title compound was a light-yellow solid obtained by referring to the synthesis method in **Example 159**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.57 (s, 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 7.83 - 7.49 (m, 1H), 6.71 (s, 1H), 4.69 - 4.58 (m, 2H), 4.22 - 4.16 (m, 2H), 3.53 - 3.43 (m, 2H), 3.36 - 3.29 (m, 2H), 3.15 - 3.06 (m, 2H), 1.50 (s, 3H), 1.37 - 1.16 (m, 6H). LC/MS (ESI) (*m/z*): 515 [M+H]⁺.

Example

161:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-(methyl-*d*₃)cyclopropyl)imidazo[1,5-*a*]pyridine-6-sulfonamide



Step 1: 1-((tert-butoxycarbonyl)amino)cyclopropane-1-carboxylic (isopropyl carbonic) anhydride

of nitrogen at 0°C, triethylamine (14 mL, 99.4 mmol) was added to the solution of 1-((tert-butoxycarbonyl)amino)cyclopropanecarboxylic acid (10 g, 49.7 mmol) in dichloromethane (100 mL); then, isopropyl chlorocarbonate (7.3 g, 59.6 mmol) was dropwise added slowly; and after dropwise adding, the reaction mixture was stirred at 0°C Under an atmosphere for 30 minutes. After completion of the reaction, the reaction mixture was quenched with ice water, and extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title compound (white solid, 7 g, yield: 47.9%).

Step 2: Tert-butyl 1-((hydroxy-*d*)methyl-*d*₃)cyclopropyl)carbamate

At 0°C, the solution of 1-((tert-butoxycarbonyl)amino)cyclopropanecarboxylic (isopropyl carbonate)formic anhydride (7 g, 24.3 mmol) in deuterio methanol (50 mL) was slowly added to deuterated sodium borohydride (1.2 g, 29.3 mmol), the reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was quenched with aqueous ammonium chloride solution, and extracted with

dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (white solid, 4 g, yield: 86.9%). ¹H NMR (400 MHz, CDCl₃) δ 5.04 (s, 1H), 1.37 (s, 9H), 0.78 - 0.73 (m, 4H).

Step 3: (1-((tert-butoxycarbonyl)amino)cyclopropyl)methyl-d₂ methanesulfonate

At 0°C, triethylamine (6.6 mL, 47.3 mmol) was added to the solution of (1-((hydroxy-d)methyl-d₂)cyclopropyl)aminotert-butyl formate (3 g, 15.8 mmol) in dichloromethane (30 mL); then, methanesulfonyl chloride (2.7 g, 23.7 mmol) was dropwise added slowly; and the mixture was continued to be stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was quenched with ice water, and extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-40% ethyl acetate) to obtain the title compound (white solid, 4 g, yield: 95.2%). ¹H NMR (400 MHz, CDCl₃) δ 3.06 - 3.03 (m, 3H), 1.47 (s, 9H), 0.98 - 0.93 (m, 4H).

Step 4: Tert-butyl (1-(iodomethyl-d₂)cyclopropyl)carbamate

At 0°C, sodium iodide (1.6 g, 10.8 mmol) was added to the solution of (1-((tert-butoxycarbonyl)amino)cyclopropyl)methyl-d₂methanesulfonate (1g, 3.6 mmol) in acetone (10 mL); and the mixture was stirred at 50°C for 4 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title compound (white solid, 600 mg, yield: 54.5%), LC/MS (ESI) (m/z): 244 (M-56+H)⁺.

Step 5: Tert-butyl (1-(methyl-d₃)cyclopropyl)carbamate

Under an atmosphere of nitrogen, palladium hydroxide (100 mg) with the mass fraction of 10% and triethylamine (0.5 mL, 3.6 mmol) were added to the solution of (1-iodomethyl-d₂)cyclopropyl)aminotert-butyl formate (600 mg, 2 mmol) in deuterio methanol (6 mL). The reaction mixture was replaced three times with deuterium and then stirred at 50°C for 6 hours under an atmosphere of deuterium at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (white solid, 360 mg, yield: 99%). LC/MS (ESI) (m/z): 119 [M+H]⁺.

Step 6: 1-(methyl-d₃)-cyclopropan-1-amine hydrochloride

1-(methyl-d₃)cyclopropylaminotert-butyl formate (200 mg, 1.1 mmol) was dissolved in 1,4-dioxane (1 mL); hydrochloric acid-dioxane (1 mL, 4M) was dropwise added slowly at room temperature; and the mixture was stirred at 40°C for 2 hours. After completion of the reaction, the reaction mixture was concentrated under

reduced pressure to obtain a crude title compound (light yellow solid, 200 mg, yield: 100%), which was directly used in the next step of reaction.

Step

7:

1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(methyl-d₃)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, triethylamine (0.5 mL) and 1-bromo-8-chloro-3-(5-difluoromethyl-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride (200 mg, 0.43 mmol) were sequentially added to the solution of 1-(methyl-d₃)-cyclopropyl-1-amine hydrochloride (200 mg, 1.1 mmol) in dichloromethane (3 mL); and the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was added with ice water for quenching, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure; and the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 35 mg, yield: 16.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.83 (d, *J* = 1.1 Hz, 1H), 8.51 (s, 1H), 7.71 (t, *J* = 53.0 Hz, 2H), 7.54 (d, *J* = 1.0 Hz, 1H), 1.56 - 1.35 (m, 4H). LC/MS (ESI) (*m/z*): 501 [M+H]⁺.

Step

8:

8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-(methyl-d₃)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, Pd/C (10 mg, mass fraction: 10%) was added to the solution of 1-bromo-8-chloro-3-(5-difluoromethyl-1,3,4-thiadiazol-2-yl)-N-(1-(methyl-d₃)cyclopropyl)imidazo[1,5-a]pyridin-6-sulfonamide (35 mg, 0.07 mmol) in ethanol (5 mL); The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 2 hours under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the mixture was filtered. The filtrate was concentrated under reduced pressure to obtain the title compound (yellow solid, 25 mg, yield: 86.2%). LC/MS (ESI) (*m/z*): 423 [M+H]⁺.

Step

9:

8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-N-(1-(methyl-d₃)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, potassium carbonate (40 mg, 0.3 mmol) and 1-(chloromethyl)-4-methoxybenzene (28 mg, 0.18 mmol) were added to the solution of 8-chloro-3-(5-difluoromethyl-1,3,4-thiadiazol-2-yl)-N-(1-(deuteriomethyl)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.12 mmol) in N,N- (1 mL); and the reaction mixture was stirred at 40°C for 6 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-15% ethyl acetate) to obtain the title compound (white solid, 30 mg, yield: 46.8%). LC/MS (ESI) (m/z): 543 [M+H]⁺.

Step

10:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-(methyl-d₃)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, cesium carbonate (54 mg, 0.16 mmol), Ruphos (5 mg, 0.011 mmol) and Ruphos Pd G3 (5 mg, 0.005 mmol) were sequentially added to the solution of 8-chloro-3-(5-difluoromethyl-1,3,4-thiadiazol-2-yl)-N-(1-(methyl-d₃)cyclopropyl)-N-(4-methoxybenzyl)imidazo[1,5-a]pyridine-6-sulfonamide (30 mg, 0.055 mmol) and 1-(2-methylacetyl)-piperazine (13 mg, 0.083 mmol) in 1,4-dioxane (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 60°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched by adding water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 30 mg, yield: 82.1%). LC/MS (ESI) (m/z): 663 [M+H]⁺.

Step

11:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-(methyl-d₃)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

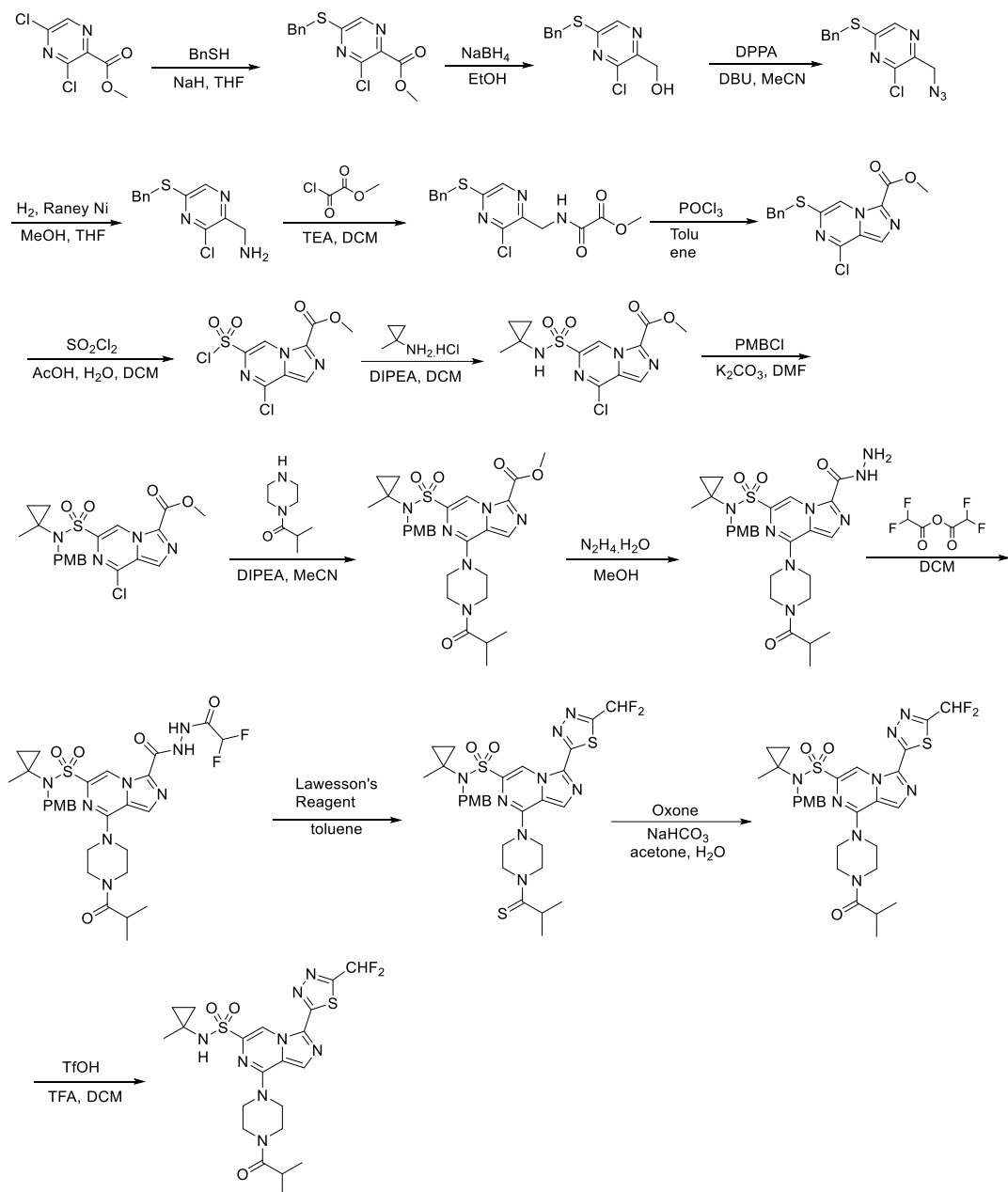
At 0°C, trifluoroacetic acid (0.1 mL) and trifluoromethanesulfonic acid (0.1 mL) was added to the solution of

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-(methyl-d₃)cyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (30 mg, 0.045 mmol) in dichloromethane (2 mL); and the reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (white solid, 7 mg, yield: 30.4%). ¹H NMR (400 MHz, CD₃OD) δ 9.82 (s, 1H), 7.92 (s, 1H), 7.50 - 7.15 (m, 1H), 6.72 (s, 1H), 3.91 - 3.79 (m, 4H), 3.44 - 3.33 (m, 4H), 3.08 - 2.98 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 6H), 0.85 - 0.76 (m, 2H), 0.53 - 0.46 (m, 2H). LC/MS (ESI) (m/z): 543 [M+H]⁺.

Example

162:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Methyl 5-(benzylthio)-3-chloropyrazine-2-carboxylate

At 0°C, sodium hydride (1.2 g, 29.0 mmol, 60% dispersed in paraffins) was added portionwise to the solution of 3,5-dichloropyrazin-2-yl methyl carboxylate (5 g, 24.2 mmol) in tetrahydrofuran (50 mL). The reaction mixture was stirred at 0°C for 30 minutes under an atmosphere of nitrogen. Then, benzyl mercaptane was dropwise added slowly (3 g, 24.2 mmol). After dropwise adding, the reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, saturated ammonium chloride solution was dropwise added slowly to quench the reaction mixture, which was then extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title

compound (colorless liquid, 5.5 g, yield: 77.3%). ¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 7.45 - 7.35 (m, 2H), 7.32 - 7.23 (m, 3H), 4.41 (s, 2H), 3.96 (s, 3H). LC/MS (ESI) (m/z): 295 [M+H]⁺.

Step 2: (5-(benzylthio)-3-chloropyrazin-2-yl) methanol

At 0°C, sodium borohydride (770 mg, 22.9 mmol) was added portionwise to the solution of 5-(benzylthio)-3-chloropyrazin-2-methyl carboxylate (4.5 g, 15.3 mmol) in ethanol (40 mL). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, ice water was dropwise added slowly to quench the reaction mixture, which was then concentrated under reduced pressure to remove ethanol. The reaction mixture was extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (colorless oil, 3.5 g, yield: 86.0%). LC/MS (ESI) (m/z): 267 [M+H]⁺.

Step 3: 2-(azidomethyl)-5-(benzylthio)-3-chloropyrazine

At 0°C, 1,8-diazabicyclo[5.4.0]undec-7-ene (3.0 g, 19.7 mmol) and azidodiphenyl phosphate (3.6 g, 13.1 mmol) were slowly added to the solution of (5-(benzylthio)-3-chloropyrazin-2-yl) methanol (3.5 g, 13.1 mmol) in acetonitrile (35 mL). The reaction mixture was stirred at room temperature for 4 hours. After completion of the reaction, the reaction mixture was extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-3% ethyl acetate) to obtain the title compound (yellow oil, 1.4 g, yield: 36.6%). LC/MS (ESI) (m/z): 292 [M+H]⁺.

Step 4: (5-(benzylthio)-3-chloropyrazin-2-yl)methanamine

Under an atmosphere of nitrogen at room temperature, raney nickel (200 mg) was added to the solution of 2-(azidomethyl)-5-(benzylthio)-3-chloropyrazine (1.3 g, 4.47 mmol) in methanol (8 mL) and tetrahydrofuran (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 18 hours under an atmosphere of hydrogen at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-10% methanol) to obtain the title compound (green solid, 780 mg, yield: 65.9%). LC/MS (ESI) (m/z): 266 [M+H]⁺.

Step 5: Methyl 2-(((5-(benzylthio)-3-chloropyrazin-2-yl)methyl)amino)-2-oxoacetate

At 0°C, triethylamine (445 mg, 4.40 mmol) and methyl oxalyl chloride (360 mg, 2.93 mmol) were slowly added to the solution of (5-(benzylthio)-3-chloropyrazin-2-yl) formamide (780 mg, 2.93 mmol) in dichloromethane (8 mL). The reaction mixture was stirred at room temperature for 0.5 hour. After completion of the reaction, the reaction mixture was diluted with dichloromethane; and the organic phase

was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 720 mg, yield: 69.7%). LC/MS (ESI) (m/z): 352 [M+H]⁺.

Step 6: Methyl 6-(benzylthio)-8-chloroimidazo[1,5-a]pyrazine-3-carboxylate

Under an atmosphere of nitrogen at 0°C, phosphorus oxychloride (5 mL) was slowly added to the solution of 2-((5-(benzylthio)-3-chloropyrazin-2-yl)methyl)amino)-2-methyl oxyacetate (720 mg, 2.05 mmol) in toluene (5 mL). The reaction mixture was stirred at 110°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane; the organic phase was washed with saturated aqueous sodium bicarbonate solution and saturated brine respectively, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 330 mg, yield: 48.3%). LC/MS (ESI) (m/z): 334 [M+H]⁺.

Step 7: Methyl 8-chloro-6-(chlorosulfonyl)imidazo[1,5-a]pyrazine-3-carboxylate

At 0°C, sulfonyl chloride (534 mg, 3.96 mmol) was dropwise added slowly to the solution of 6-(benzylthio)-8-chloroimidazo[1,5-a]pyrazin-3-methyl carboxylate (330 mg, 0.99 mmol) in dichloromethane (4 mL), water (0.4 mL) and acetic acid (0.2 mL). The reaction mixture was stirred at room temperature for 0.5 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane, sequentially washed with saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 307 mg, yield: 100%), which was directly used in the next step of reaction without purification.

Step 8: Methyl 8-chloro-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyrazine-3-carboxylate

At 0°C, N,N-diisopropylethylamine (0.43 mL, 2.47 mmol) and 8-chloro-6-(chlorosulfonyl)imidazo[1,5-a]pyrazin-3-methyl carboxylate (307 mg, 0.989 mmol) were slowly added to the solution of 1-methylcyclopropan-1-amine hydrochloride (160 mg, 1.48 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 0.5 hour. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-28% ethyl acetate) to obtain the title compound (yellow solid, 160 mg, yield: 46.9%). LC/MS (ESI) (m/z): 345 [M+H]⁺.

Step

9:

Methyl

8-chloro-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyrazine-3-carbox

ylate

At room temperature, potassium carbonate (192 mg, 1.39 mmol) and 1-(chloromethyl)-4-methoxybenzene (109 mg, 0.696 mmol) were added to the solution of 8-chloro-6-(N-(1-methylcyclopropyl)sulfonamideformyl)imidazo[1,5-a]pyrazin-3-methyl carboxylate (160 mg, 0.464 mmol) in N,N-dimethylformamide (2 mL). The reaction mixture was stirred at 45°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 155 mg, yield: 71.8%). LC/MS (ESI) m/z: 465 [M+H]⁺.

Step 10: Methyl 8-(4-isobutyrylpiperazin-1-yl)-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyrazine-3-carboxylate

At room temperature, N,N-diisopropylethylamine (0.16 mL, 0.94 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (73 mg, 0.468 mmol) were added to the solution of 8-chloro-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfanilamido)imidazo[1,5-a]pyrazin-3-methyl carboxylate (145 mg, 0.312 mmol) in acetonitrile (2 mL). The reaction mixture was stirred at 45°C for 4 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-10% methanol) to obtain the title compound (yellow solid, 170 mg, yield: 93.2%). LC/MS (ESI) m/z: 585 [M+H]⁺.

Step 11: 3-(hydrazinecarbonyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyrazine-6-sulfonamide

At room temperature, hydrazine hydrate (0.18 mL, 2.91 mmol) with the mass fraction of 80% was added to the solution of 8-(4-isobutyrylpiperazin-1-yl)-6-(N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)sulfanilamido)imidazo[1,5-a]pyrazin-3-methyl carboxylate (170 mg, 0.291 mmol) in methanol (2 mL). The reaction mixture was stirred at 75 °C for 1 hour. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 170 mg, yield: 78.5%), which was directly used in the next step of reaction without purification. LC/MS (ESI) m/z: 585 [M+H]⁺.

Step 12: 3-(2-(2,2-difluoroacetyl)hydrazine-1-carbonyl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyrazine-6-sulfonamide

At 0°C, difluoroacetic anhydride (0.036 mL, 0.291 mmol) was slowly added to the solution of 3-(hydrazinocarbonyl)-8-(4-isobutylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyrazin-6-sulfonamide (170 mg, 0.291 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at 0 °C for 0.5 hour. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; and the residue was purified by column chromatography (eluent: dichloromethane/methanol, gradient: 0-10% methanol) to obtain the title compound (yellow solid, 160 mg, yield: 83.0%). LC/MS (ESI) m/z: 663 [M+H]⁺.

Step

13:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)-8-(4-(2-methylpropanethioyl)piperazin-1-yl)imidazo[1,5-a]pyrazine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, the Lawesson's reagent (34 mg, 0.083 mmol) was added to the solution of 3-(2-(2,2-difluoroacetyl)hydrazin-1-carbonyl)-8-(4-isobutylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyrazin-6-sulfonamide (50 mg, 0.075 mmol) in toluene (2 mL). The reaction mixture was stirred at 110°C for 18 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow solid, 20 mg, yield: 39.4%). LC/MS (ESI) m/z: 677 [M+H]⁺.

Step

14:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyrazine-6-sulfonamide

At 0°C, sodium bicarbonate (7 mg, 0.089 mmol) and potassium hydrogen persulfate (51 mg, 0.059 mmol) were slowly added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)-8-(4-(2-methylpropylthio)piperazin-1-yl)imidazo[1,5-a]pyrazin-6-sulfonamide (20 mg, 0.030 mmol) in acetone (1.5 mL) and water (0.5 mL). The reaction mixture was stirred at room temperature for 0.5 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane; and the organic phase was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow solid, 12 mg, yield: 61.5%). LC/MS (ESI) m/z: 661 [M+H]⁺.

Step

15:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)imi

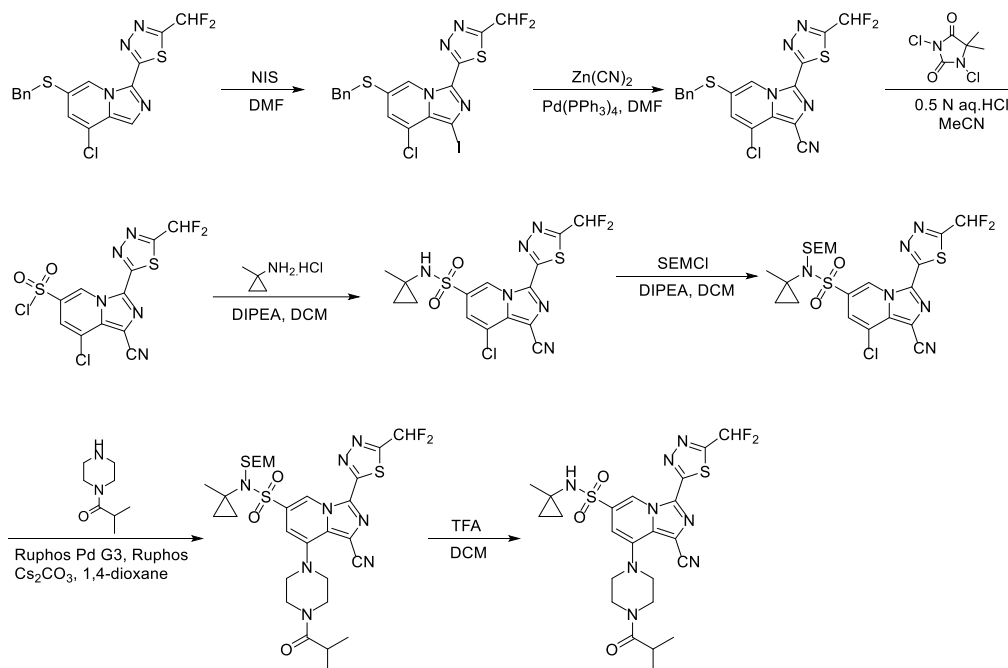
dazo[1,5-a]pyrazine-6-sulfonamide

At 0°C, trifluoroacetic acid (0.5 mL) and trifluoromethanesulfonic acid (0.1 mL) were dropwise added slowly to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutylpiperazin-1-yl)-N-(4-methoxybenzyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyrazin-6-sulfonamide (12 mg, 0.018 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 3.5 mg, yield: 35.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 8.33 (d, *J* = 10.5 Hz, 2H), 7.70 (t, *J* = 53.1 Hz, 1H), 4.10 - 3.98 (m, 4H), 3.78 - 3.67 (m, 4H), 2.96 - 2.87 (m, 1H), 1.20 (s, 3H), 1.04 (d, *J* = 6.6 Hz, 6H), 0.81 - 0.75 (m, 2H), 0.47 - 0.41 (m, 2H). LC/MS (ESI) (*m/z*): 541 [M+H]⁺.

Example

163:

1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

2-(6-(benzylthio)-8-chloro-1-iodoimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole

At room temperature, N-iodosuccinimide (275 mg, 1.22 mmol) was added to the solution of 2-(6-(benzylthio)-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (500 mg, 1.22 mmol) in N,N-dimethylformamide (5 mL). The reaction mixture was stirred at 70°C for 18 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue

was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 380 mg, yield: 58.1%). LC/MS (ESI) m/z: 535 [M+H]⁺.

Step

2:

6-(benzylthio)-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-1-carbonitrile

At room temperature, tetrakis(triphenylphosphine)palladium (164 mg, 0.142 mmol) was added to the solution of 2-(6-(benzylthio)-8-chloro-1-iodoimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (380 mg, 0.711 mmol) and zinc cyanide (167 mg, 1.42 mmol) in N,N-dimethylformamide (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 100°C for 5 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25 % ethyl acetate) to obtain the title compound (yellow solid, 160 mg, yield: 51.9%). LC/MS (ESI) m/z: 434 [M+H]⁺.

Step 3: 8-chloro-1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride

At 0°C, dichlorohydantoin (291 mg, 1.48 mmol) was added to the solution of 6-(benzylthio)-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-1-nitrile (160 mg, 0.369 mmol) in acetonitrile (2 mL), 1N hydrochloric acid (0.5 mL) and water (0.5 mL). The reaction mixture was stirred at room temperature for 10 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 151 mg, yield: 100%), which was directly used in the next step of reaction without purification.

Step

4:

8-chloro-1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) and 8-chloro-1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride (151 mg, 0.37 mmol) were added to the solution of 1-methylcyclopropan-1-amine hydrochloride (60 mg, 0.55 mmol) in dichloromethane (2 mL); and the reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30%

ethyl acetate) to obtain the title compound (yellow solid, 70 mg, yield: 42.7%). LC/MS (ESI) (m/z): 445 [M+H]⁺.

Step

5:

8-chloro-1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, N,N-diisopropylethylamine (61 mg, 0.472 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (39 mg, 0.236 mmol) were added to the solution of 8-chloro-1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (70 mg, 0.157 mmol) in N,N-dimethylformamide (2 mL). The reaction mixture was stirred at 0°C for 10 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, sequentially washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-25 % ethyl acetate) to obtain the title compound (yellow solid, 70 mg, yield: 77.4%). LC/MS (ESI) m/z: 575 [M+H]⁺.

Step

6:

1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen at room temperature, cesium carbonate (79 mg, 0.244 mmol), Ruphos (11 mg, 0.024 mmol) and Ruphos Pd G3 (10 mg, 0.012 mmol) were added to the solution of 8-chloro-1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (70 mg, 0.122 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (38 mg, 0.244 mmol) in 1,4-dioxane (3 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 85°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, added with water, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the title compound (yellow solid, 50 mg, yield: 59.1%). LC/MS (ESI) m/z: 695 [M+H]⁺.

Step

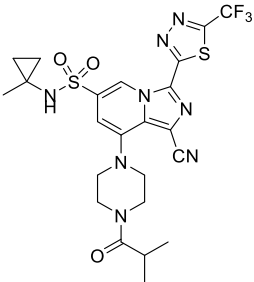
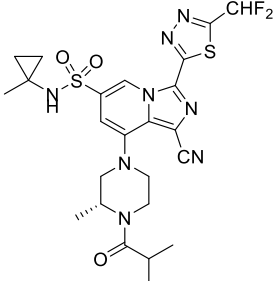
7:

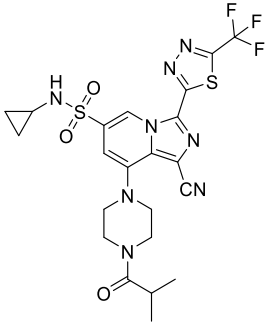
1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (1 mL) was dropwise added slowly to the solution of 1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.072 mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature for 30 minutes. The reaction mixture

was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 18.5 mg, yield: 45.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.74 (s, 1H), 8.59 (s, 1H), 7.72 (t, *J* = 53.1 Hz, 1H), 7.19 (s, 1H), 3.86 - 3.72 (m, 4H), 3.22 - 3.10 (m, 4H), 3.02 - 2.93 (m, 1H), 1.16 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 6H), 0.77 - 0.70 (m, 2H), 0.50 - 0.43 (m, 2H). LC/MS (ESI) (*m/z*): 565 [M+H]⁺.

By referring to the preparation method in Example 163, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

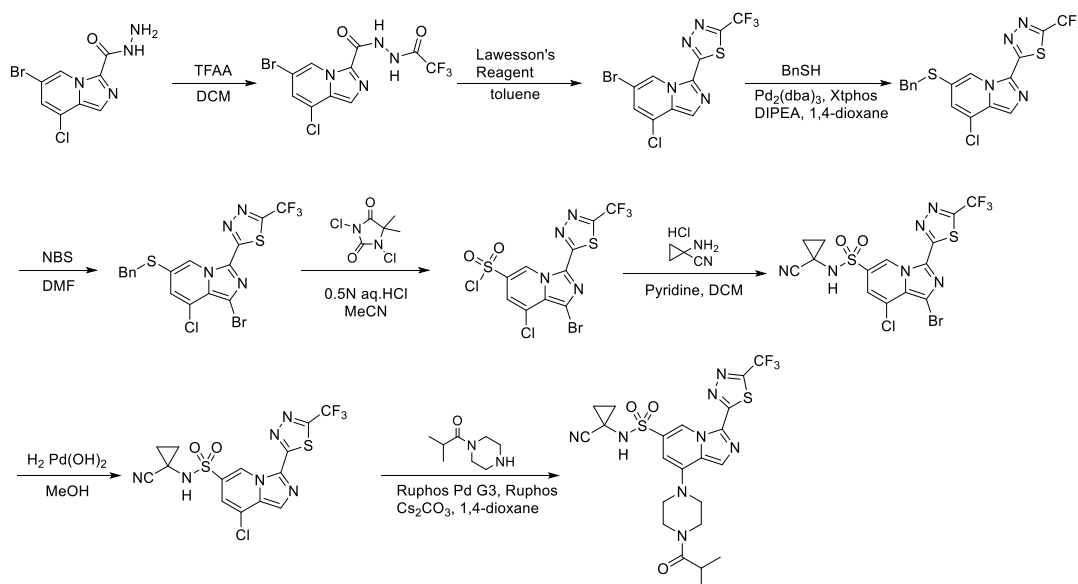
Example	Structure and name	Analysis data
Example 164	 1-cyano-8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.71 (s, 1H), 8.61 (s, 1H), 7.22 (s, 1H), 3.86 - 3.75 (m, 4H), 3.22 - 3.12 (m, 4H), 3.00 - 2.94 (m, 1H), 1.17 (s, 3H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H), 0.77 - 0.71 (m, 2H), 0.50 - 0.44 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 583 [M+H] ⁺ .
Example 165	 (R)-1-cyano-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.74 (s, 1H), 8.60 (s, 1H), 7.73 (t, <i>J</i> = 53.1 Hz, 1H), 7.19 (s, 1H), 4.93 - 4.28 (m, 1H), 4.01 - 3.81 (m, 1H), 3.70 (d, <i>J</i> = 12.4 Hz, 1H), 3.21 - 3.07 (m, 3H), 3.00 - 2.77 (m, 2H), 1.51 - 1.32 (m, 3H), 1.18 (s, 3H), 1.05 (d, <i>J</i> = 6.6 Hz, 6H), 0.77 - 0.72 (m, 2H), 0.50 - 0.45 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 579 [M+H] ⁺ .

Example 166	 1-cyano-N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.74 (s, 1H), 8.40 (s, 1H), 7.22 (s, 1H), 3.88 - 3.77 (m, 4H), 3.24 - 3.16 (m, 4H), 3.01 - 2.95 (m, 1H), 2.34 - 2.29 (m, 1H), 1.08 - 1.04 (m, 6H), 0.57 - 0.49 (m, 4H). LC/MS (ESI) (m/z): 569 [M+H] ⁺ .
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Example

167:

N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: 6-bromo-8-chloro-N'-(2,2,2-trifluoroacetyl)imidazo[1,5-a]pyridine-3-carbohydrazide

Under an atmosphere of nitrogen, trifluoroacetic anhydride (435 mg, 2.07 mmol) was added to the solution of 6-bromo-8-chloroimidazo[1,5-a]pyridine-3-carbohydrazide (600 mg, 2.07 mmol) in dichloromethane (6 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-15% ethyl acetate) to obtain the title compound (yellow solid, 600 mg, yield: 75.1%). LC/MS (ESI) (m/z): 385 [M+H]⁺.

Step 2: 2-(6-bromo-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole

Under an atmosphere of nitrogen, the Lawesson's reagent (692 mg, 1.71 mmol) was added to the solution of 6-bromo-8-chloro-N'-(2,2,2-trifluoroacetyl)imidazo[1,5-a]pyridin-3-carbohydrazide (600 mg, 1.56 mmol) in anhydrous toluene (6 mL). The reaction mixture was stirred at 110°C for 4 hours. After completion of the reaction, sodium bicarbonate was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-20% ethyl acetate) to obtain the title compound (yellow solid, 500 mg, yield: 83.7%). LC/MS (ESI) (m/z): 383 [M+H]⁺.

Step 3: 2-(6-(benzylthio)-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole

Under an atmosphere of nitrogen, N,N-diisopropylethylamine (505 mg, 3.91 mmol), Xantphos (151 mg, 0.26 mmol), Pd₂(dba)₃ (119 mg, 0.13 mmol) were sequentially added to the solution of 2-(6-bromo-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole (500 mg, 1.30 mmol) and benzyl mercaptane (0.15 mL, 1.30 mmol) in 1,4-dioxane (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 510 mg, yield: 91.6%). LC/MS (ESI) (m/z): 427 [M+H]⁺.

Step

4:

2-(6-(benzylthio)-1-bromo-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole

At 0°C, NBS (213 mg, 1.20 mmol) was added to the solution of 2-(6-(benzylthio)-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole (510 mg, 1.20 mmol) in N,N-dimethylformamide (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 550 mg, yield: 91.2%). LC/MS (ESI) (m/z): 505 [M+H]⁺.

Step

5:

1-bromo-8-chloro-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride

At 0°C, 1N hydrochloric acid (1.25 mL), water (1.25 mL) and dichlorohydantoin (643 mg, 3.27 mmol) were sequentially added to the solution of 2-(6-(benzylthio)-1-bromo-8-chloroimidazo[1,5-a]pyridin-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole (550

mg, 1.10 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at 0°C for 10 minutes. After completion of the reaction, water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was pulped with petroleum ether, and then dried in vacuum to obtain the title compound (yellow solid, 520 mg, yield: 99.2%). LC/MS (ESI) (m/z): 481 [M+H]⁺.

Step

6:

1-bromo-8-chloro-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, anhydrous pyridine (1 mL) was added to the solution of 1-amino-1-cyclopropyl cyanic hydrochloride (255 mg, 2.16 mmol) in anhydrous dichloromethane (4 mL); and the reaction mixture was stirred at 0°C for 5 minutes. Then, 1-bromo-8-chloro-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-6-sulfonyl chloride (520 mg, 1.01 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 450 mg, yield: 79.0%). LC/MS (ESI) (m/z): 527 [M+H]⁺.

Step

7:

8-chloro-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, palladium hydroxide on carbon (40 mg) with the mass fraction of 20% was added to the solution of 1-bromo-8-chloro-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (450 mg, 0.85 mmol) in anhydrous methanol (20 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 20°C for 24 hours under an atmosphere of hydrogen at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (yellow solid, 150 mg, yield: 39.2%). LC/MS (ESI) (m/z): 449 [M+H]⁺.

Step

8:

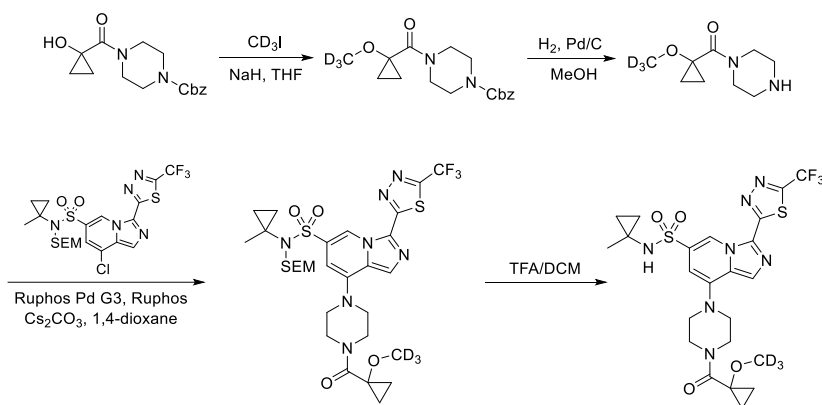
N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (101 mg, 0.31 mmol), Ruphos (14 mg, 0.031 mmol), Ruphos Pd G3 (26 mg, 0.031 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfo

namide (70 mg, 0.16 mmol) and 2-methyl-1-(piperazin-1-yl)propan-1-one (48 mg, 0.31 mmol) in 1,4-dioxane (2.1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 30 minutes under an atmosphere of nitrogen. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-50% ethyl acetate), and then purified by pre-HPLC (C18, 10-50% acetonitrile in H₂O, containing 0.1% formic acid) to further obtain the title compound (yellow solid, 32.2 mg, yield: 36.3%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (s, 1H), 9.50 (s, 1H), 8.15 (s, 1H), 6.71 (s, 1H), 3.82 - 3.72 (m, 4H), 3.40 - 3.35 (m, 4H), 2.98 - 2.92 (m, 1H), 1.51 - 1.46 (m, 2H), 1.42 - 1.35 (m, 2H), 1.05 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (*m/z*): 569 [M+H]⁺.

Example 168:

8-(4-(1-(methoxy-*d*3)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Benzyl 4-(1-(methoxy-*d*3)cyclopropane-1-carbonyl)piperazine-1-carboxylate

At 0°C, sodium hydride (160 mg, 3.94 mmol, mass fraction: 60%) was added portionwise to the solution of 4-(1-hydroxycyclopropan-1-acyl)piperazin-1-benzyl formate (400 mg, 1.31 mmol) in tetrahydrofuran (10 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was cooled to room temperature, deuteriodomethane (380 mg, 2.62 mmol) was dropwise added at 0°C, and the reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride that was cooled with ice water, and extracted with ethyl acetate twice. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (white solid, 150 mg, yield: 35.7%). LC/MS (ESI) (*m/z*): 322 [M+H]⁺.

Step 2: (1-(methoxy-*d*3)cyclopropyl)(piperazin-1-yl)methanone

Under an atmosphere of nitrogen, palladium on carbon (20 mg) with the mass fraction of 10% was added to

the solution of 4-(1-(deuteromethoxy)cyclopropan-1-acyl)piperazin-1-benzyl carboxylate (150 mg, 0.47 mmol) in ethyl acetate (8 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 3 hours under an atmosphere of hydrogen at one atmospheric pressure. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (colorless oil, 80 mg, yield: 91.1%). LC/MS (ESI) (m/z): 188 [M+H]⁺.

Step 3:

8-(4-(1-(methoxy-d3)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (87 mg, 0.27 mmol), Ruphos (8 mg, 0.02 mmol) and Ruphos Pd G3 (8 mg, 0.01 mmol) were sequentially added to the solution of 8-chloro-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.09 mmol) and (1-(deuteromethoxy)cyclopropan-1-acyl)piperazine (25 mg, 0.13 mmol) in 1,4-dioxane (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 40 mg, yield: 63.2%). LC/MS (ESI) (m/z): 719 [M+H]⁺.

Step

4:

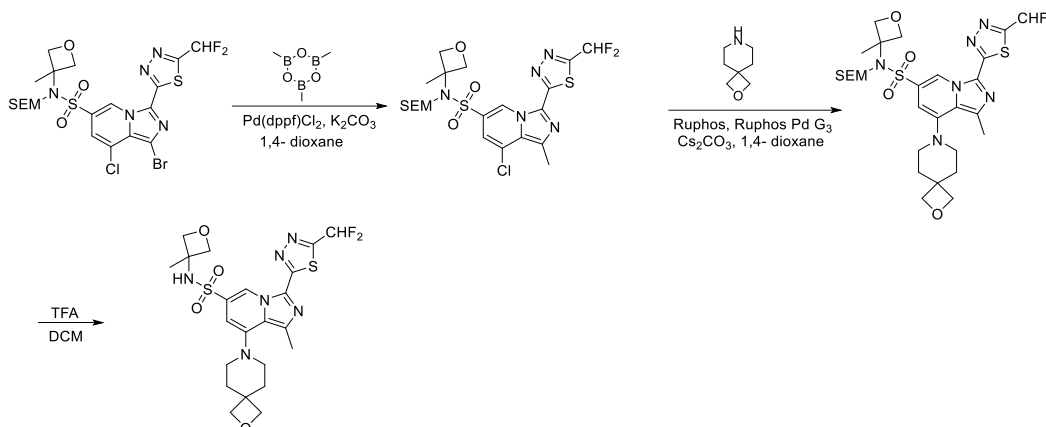
8-(4-(1-(methoxy-d3)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (2 mL) was added to the solution of (8-(4-(1-(deuteromethoxy)cyclopropan-1-acyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (40 mg, 0.06 mmol) in dichloromethane (5 mL); and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 12 mg, yield: 36.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.59 (s, 1H), 8.44 (s, 1H), 8.14 (s, 1H), 6.76 (s, 1H), 4.12 - 3.70 (m, 4H), 3.42 - 3.36 (m, 4H), 1.16 (s, 3H), 1.06 - 1.01 (m, 2H), 0.96 - 0.91 (m, 2H), 0.76 - 0.71 (m, 2H), 0.48 - 0.44 (m, 2H). LC/MS (ESI) (m/z): 589 [M+H]⁺.

Example

169:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-methyl-N-(3-methyloxetan-3-yl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-methyl-N-(3-methyloxetan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, Pd(dppf)Cl₂ (9 mg, 0.02 mmol) and potassium carbonate (120 mg, 0.69 mmol) were added to the solution of 1-bromo-8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (150 mg, 0.23 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trimethoxytriborane (0.1 ml, 0.34 mmol) in 1, 4- dioxane (2 mL) and water (0.5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, and extracted with ethyl acetate three times. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-100% ethyl acetate) to obtain the title compound (yellow solid, 50 mg, yield: 37.3%). LC/MS (ESI) (m/z): 580 [M+H]⁺.

Step

2:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-methyl-N-(3-methyloxetan-3-yl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, Ruphos (4 mg, 0.01 mmol), Ruphos Pd G₃ (4 mg, 0.01 mmol), and cesium carbonate (75 mg, 0.27 mmol) were added to the solution of 8-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-methyl-N-(3-methyloxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.09 mmol) and 2-oxa-7-azaspiro[3.5]nonane (15 mg, 0.09 mmol) in 1,4-dioxane (2 mL). of nitrogen, the reaction mixture was stirred at 80°C Under an atmosphere for 3 hours. After completion of the reaction, the reaction mixture

was diluted with ethyl acetate, washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-100% ethyl acetate) to obtain the title compound (yellow solid, 20 mg, yield: 33%). LC/MS (ESI) (m/z): 671 [M+H]⁺.

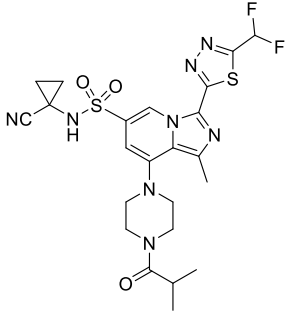
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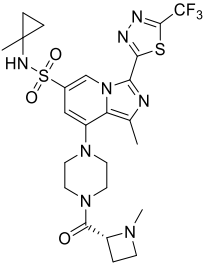
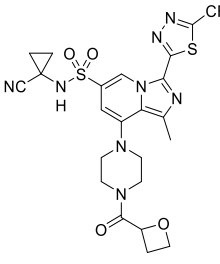
3:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-methyl-N-(3-methyloxetan-3-yl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (1 mL) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-1-methyl-N-(3-methyloxacyclobutan-3-yl)-8-(2-oxa-7-azaspiro[3.5]non-7-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (20 mg, 0.03 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at 25°C for 1 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 1.5 mg, yield: 9.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.56 (s, 1H), 8.66 (s, 1H), 7.66 (t, *J* = 53.6 Hz, 1H), 6.73 (s, 1H), 4.62 (d, *J* = 6.2 Hz, 2H), 4.40 (s, 4H), 4.17 (d, *J* = 6.3 Hz, 2H), 3.01 - 2.97 (m, 4H), 2.70 (s, 3H), 2.10 - 1.98 (m, 4H), 1.48 (s, 3H). LC/MS (ESI) (m/z): 541 [M+H]⁺.

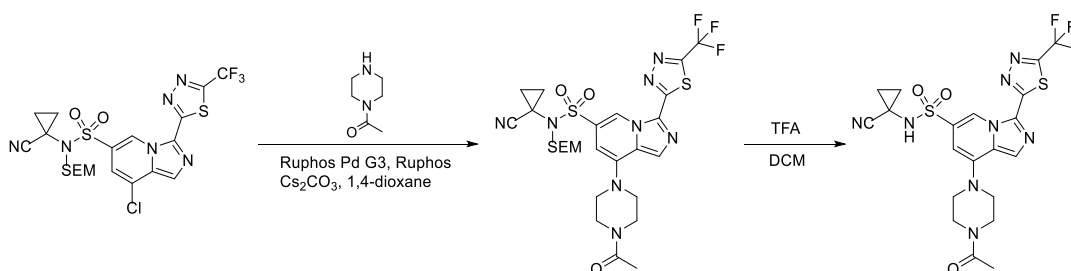
By referring to the preparation method in Example 169, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

Example	Structure and name	Analysis data
Example 170	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)-1-methylimidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.66 (s, 1H), 7.61 (t, <i>J</i> = 52.9 Hz, 1H), 6.75 (s, 1H), 3.86 – 3.67 (m, 4H), 3.12 – 3.01 (m, 4H), 2.96 – 2.92 (m, 1H), 2.74 (s, 3H), 1.46 – 1.41 (m, 2H), 1.37 – 1.32 (m, 2H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H). LC/MS (ESI) (m/z): 565 [M+H] ⁺ .

Example 171	 (R)-1-methyl-8-(4-(1-methylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.80 (s, 1H), 6.81 (s, 1H), 4.97 – 4.90 (m, 1H), 3.98 – 3.83 (m, 2H), 3.83 – 3.65 (m, 2H), 3.64 – 3.55 (m, 2H), 3.25 – 3.06 (m, 4H), 2.80 (s, 3H), 2.76 (s, 3H), 2.73 – 2.64 (m, 1H), 2.56 – 2.47 (m, 1H), 1.26 (s, 3H), 0.86 – 0.77 (m, 2H), 0.56 – 0.47 (m, 2H). LC/MS (ESI) (m/z): 600 [M+H]⁺.
Example 172	 N-(1-cyanocyclopropyl)-1-methyl-8-(4-(oxetane-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.89 (s, 1H), 6.85 (s, 1H), 5.61 – 5.49 (m, 1H), 4.75 – 4.51 (m, 2H), 4.00 – 3.69 (m, 4H), 3.66 – 3.55 (m, 2H), 3.23 – 3.17 (m, 2H), 3.02 – 2.84 (m, 2H), 2.80 (s, 3H), 1.55 – 1.52 (m, 2H), 1.47 – 1.44 (m, 2H). LC/MS (ESI) (m/z): 597 [M+H]⁺.

Example 173:

8-(4-acetypiperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1:

8-(4-acetypiperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (68 mg, 0.21 mmol), Ruphos (7 mg, 0.014 mmol) and Ruphos Pd G3 (7 mg, 0.007 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methylimidazo[1,5-a]pyridine-6-sulfonamide (40 mg, 0.07 mmol) and 1-acetypiperazine (12 mg, 0.09 mmol)

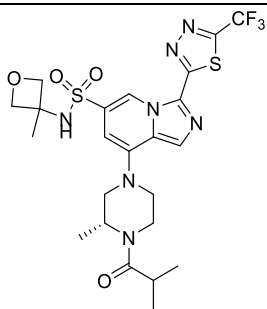
in 1,4-dioxane (3 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-20% methanol) to obtain the title compound (yellow solid, 40 mg, yield: 86.3%). LC/MS (ESI) *m/z*: 671 [M+H]⁺.

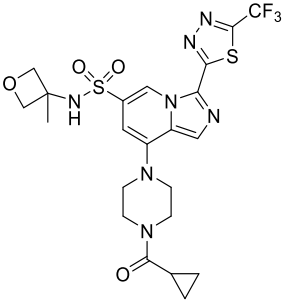
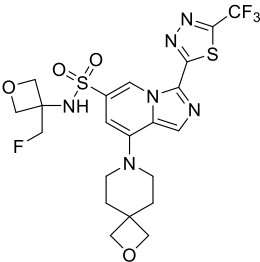
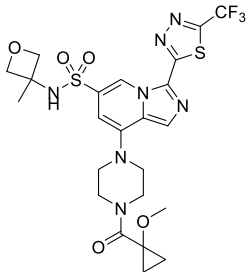
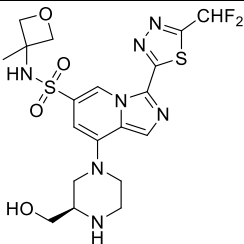
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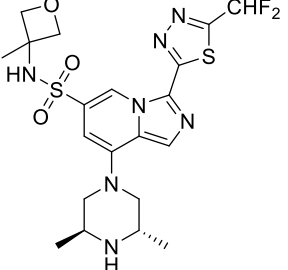
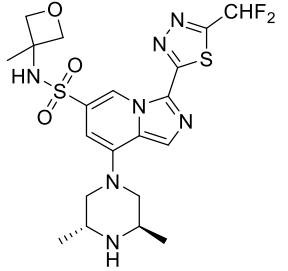
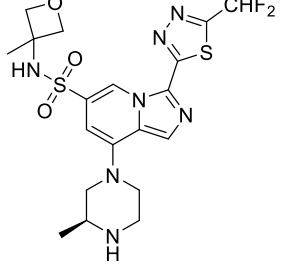
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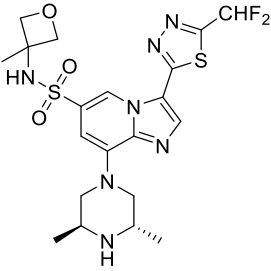
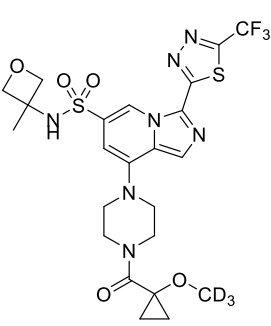
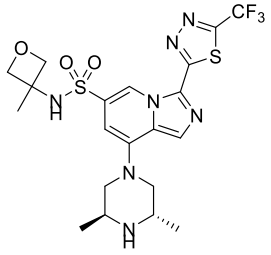
At 0°C, trifluoroacetic acid (0.5 mL) was dropwise added slowly to the solution of 8-(4-acetpiperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (40 mg, 0.06mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature for 30 minutes. The mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 8 mg, yield: 24.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (s, 1H), 8.14 (s, 1H), 6.71 (s, 1H), 3.74 – 3.69 (m, 4H), 3.45 – 3.40 (m, 4H), 2.09 (s, 3H), 1.51 – 1.46 (m, 2H), 1.41 – 1.33 (m, 2H). LC/MS (ESI) (*m/z*): 541 [M+H]⁺.

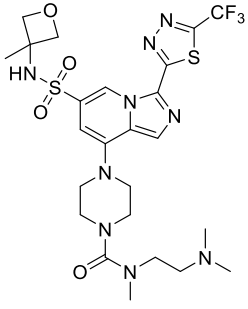
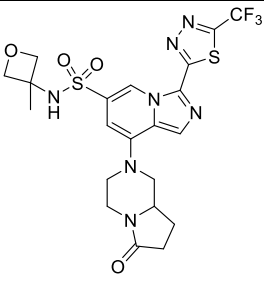
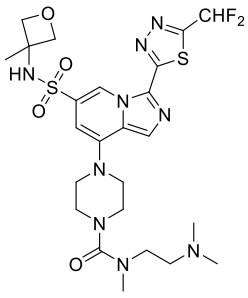
By referring to the preparation method in Example 173, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

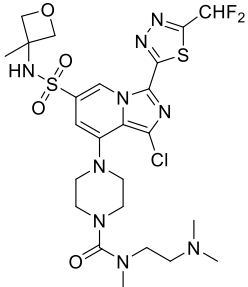
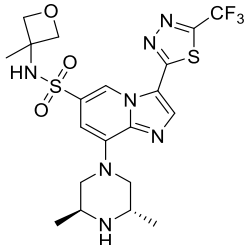
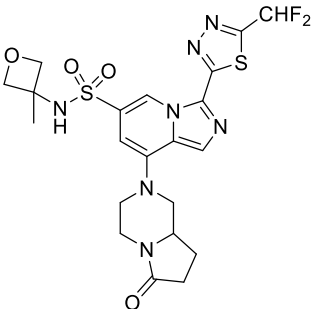
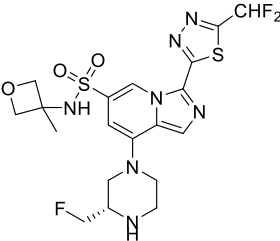
Example	Structure and name	Analysis data
Example 174	 (R)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.55 (s, 1H), 8.74 (s, 1H), 7.99 (s, 1H), 6.72 (s, 1H), 4.89 - 4.67 (m, 1H), 4.65 - 4.61 (m, 2H), 4.47 - 4.32 (m, 1H), 4.20 - 4.15 (m, 2H), 4.12 - 3.85 (m, 1H), 3.73 - 3.64 (m, 2H), 3.13 - 2.87 (m, 3H), 1.52 - 1.43 (m, 3H), 1.37 - 1.25 (m, 3H), 1.08 - 1.00 (d, <i>J</i> = 6.5 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 588 [M+H] ⁺ .

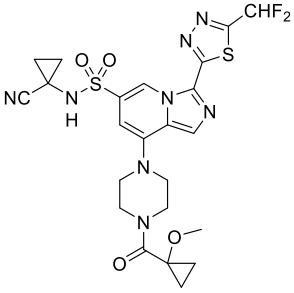
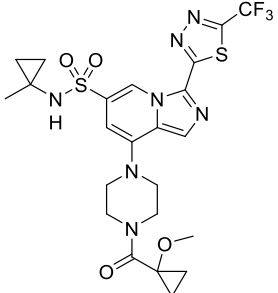
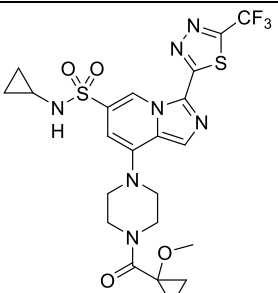
Example 175	 8-(4-(cyclopropanecarbonyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.56 (s, 1H), 8.74 (s, 1H), 8.11 (s, 1H), 6.73 (s, 1H), 4.63 (d, <i>J</i> = 6.1 Hz, 2H), 4.18 (d, <i>J</i> = 6.2 Hz, 2H), 4.03 - 3.88 (m, 2H), 3.80 - 3.66 (m, 2H), 3.45 - 3.37 (m, 2H), 3.33 - 3.30 (m, 2H), 2.10 - 2.00 (m, 1H), 1.50 (s, 3H), 0.81 - 0.72 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 572 [M+H]⁺.
Example 176	 N-(3-(fluoromethyl)oxetan-3-yl)-8-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.53 (s, 1H), 9.06 (s, 1H), 8.02 (s, 1H), 6.74 (s, 1H), 4.71 (s, 1H), 4.65 - 4.60 (m, 2H), 4.59 (s, 1H), 4.44 - 4.39 (m, 4H), 4.38 - 4.35 (m, 2H), 3.28 - 3.21 (m, 4H), 2.07 - 2.00 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 563 [M+H]⁺.
Example 177	 8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.56 (s, 1H), 8.72 (s, 1H), 8.12 (s, 1H), 6.76 (s, 1H), 4.63 (d, <i>J</i> = 6.1 Hz, 2H), 4.18 (d, <i>J</i> = 6.3 Hz, 2H), 4.09 - 3.70 (m, 4H), 3.41 - 3.37 (m, 4H), 3.27 (s, 3H), 1.49 (s, 3H), 1.08 - 0.99 (m, 2H), 0.97 - 0.89 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 602 [M+H]⁺.
Example 178		¹H NMR (400 MHz, CD₃OD) δ 9.84 (s, 1H), 7.92 (s, 1H), 7.33 (t, <i>J</i> = 53.5 Hz, 1H), 6.81 (s, 1H), 4.79 (d, <i>J</i> = 6.3 Hz, 2H), 4.32 (d, <i>J</i> = 6.5 Hz, 2H), 3.87 - 3.81 (m, 3H), 3.79 - 3.74 (m, 1H), 3.55 - 3.50 (m, 1H), 3.45 - 3.35 (m, 2H),

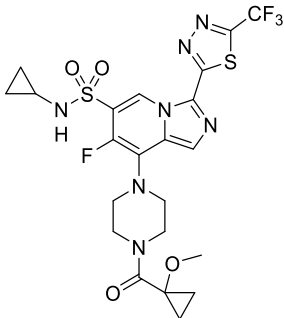
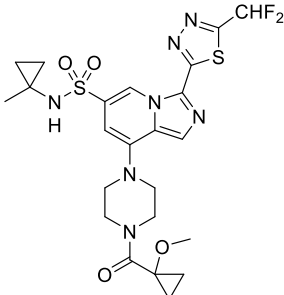
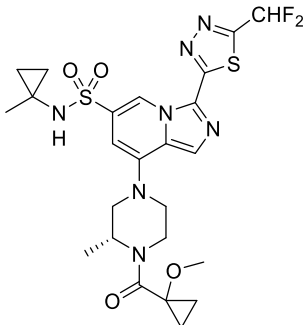
	(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(hydroxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	3.21 - 3.15 (m, 1H), 3.12 - 3.06 (m, 1H), 1.64 (s, 3H). LC/MS (ESI) (m/z): 516 [M+H] ⁺ .
Example 179	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.85 (s, 1H), 7.86 (s, 1H), 7.33 (t, <i>J</i> = 53.5 Hz, 1H), 4.80 - 4.79 (m, 2H), 4.33 - 4.31 (m, 2H), 3.75 - 3.69 (m, 2H), 3.49 - 3.45 (m, 2H), 3.28 - 3.22 (m, 2H), 1.64 (s, 3H), 1.46 (d, <i>J</i> = 6.6 Hz, 6H). LC/MS (ESI) (m/z): 514 [M+H] ⁺ .
Example 180	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5R)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.62 (s, 1H), 8.96 (s, 1H), 8.74 (s, 1H), 8.01 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.79 (s, 1H), 4.67 - 4.61 (m, 2H), 4.22 - 4.17 (m, 2H), 3.94 - 3.85 (m, 2H), 3.53 - 3.48 (m, 2H), 3.29 - 3.24 (m, 2H), 1.51 (s, 3H), 1.47 - 1.44 (m, 3H), 1.43 - 1.41 (m, 3H). LC/MS (ESI) (m/z): 514 [M+H] ⁺ .
Example 181	 (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.85 (d, <i>J</i> = 3.1 Hz, 1H), 7.91 (d, <i>J</i> = 2.2 Hz, 1H), 7.26 (t, <i>J</i> = 53.5 Hz, 1H), 6.80 (s, 1H), 4.79 (d, <i>J</i> = 6.1 Hz, 2H), 4.32 (d, <i>J</i> = 5.7 Hz, 2H), 3.86 - 3.80 (m, 2H), 3.54 - 3.41 (m, 3H), 3.17 - 3.11 (m, 1H), 2.93 - 2.87 (m, 1H), 1.64 (s, 3H), 1.45 - 1.34 (m, 4H). LC/MS (ESI) (m/z): 500 [M+H] ⁺ .

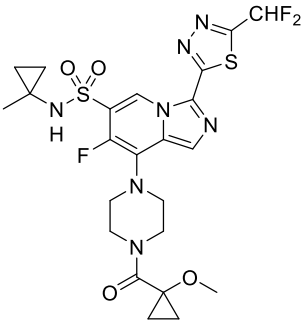
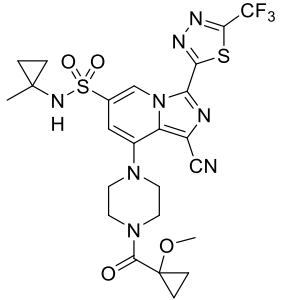
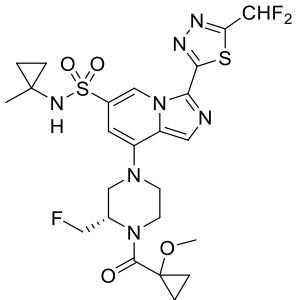
Example 182	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.93 (d, <i>J</i> = 1.5 Hz, 1H), 8.45 (s, 1H), 7.35 (t, <i>J</i> = 53.5 Hz, 1H), 7.11 (d, <i>J</i> = 1.5 Hz, 1H), 4.79 (d, <i>J</i> = 6.3 Hz, 2H), 4.32 (d, <i>J</i> = 6.6 Hz, 2H), 3.84 - 3.79 (m, 4H), 3.58 - 3.53 (m, 2H), 1.64 (s, 3H), 1.46 (d, <i>J</i> = 6.5 Hz, 7H). LC/MS (ESI) (<i>m/z</i>): 514 [M+H]⁺.
Example 183	 8-(4-(1-(methoxy-d₃)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.57 (s, 1H), 8.73 (s, 1H), 8.14 (s, 1H), 6.77 (s, 1H), 4.65 - 4.62 (m, 2H), 4.20 - 4.17 (m, 2H), 4.01 - 3.69 (m, 4H), 3.42 - 3.35 (m, 4H), 1.50 (s, 3H), 1.05 - 1.01 (m, 2H), 0.95 - 0.91 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 605 [M+H]⁺.
Example 184	 8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.85 (d, <i>J</i> = 7.3 Hz, 1H), 7.91 (d, <i>J</i> = 4.7 Hz, 1H), 6.86 (s, 1H), 4.82 - 4.76 (m, 2H), 4.37 - 4.29 (m, 2H), 4.03 - 3.94 (m, 2H), 3.65 - 3.58 (m, 2H), 3.41 - 3.35 (m, 2H), 1.65 (s, 3H), 1.59 - 1.55 (m, 6H). LC/MS (ESI) (<i>m/z</i>): 532 [M+H]⁺.

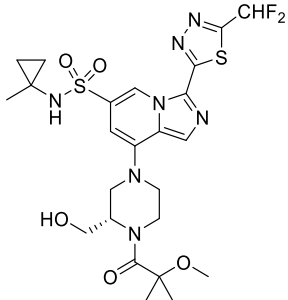
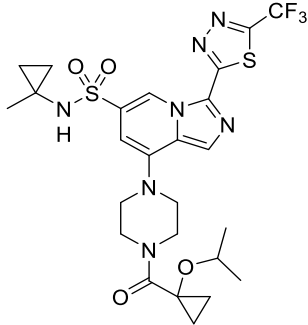
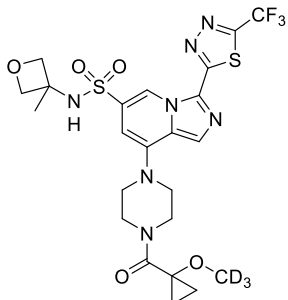
Example 185	 N-(2-(dimethylamino)ethyl)-N-methyl-4-(6-(N-(3-methyloxetan-3-yl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperazine-1-carboxamide	¹H NMR (400 MHz, CD₃OD) δ 9.81 (d, <i>J</i> = 4.7 Hz, 1H), 7.93 (d, <i>J</i> = 3.5 Hz, 1H), 6.78 (d, <i>J</i> = 1.7 Hz, 1H), 4.81 - 4.77 (m, 2H), 4.36 - 4.30 (m, 2H), 3.64 - 3.59 (m, 4H), 3.57 - 3.53 (m, 2H), 3.44 - 3.39 (m, 4H), 3.38 - 3.35 (m, 2H), 3.04 (s, 3H), 2.99 - 2.97 (m, 6H), 1.65 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 632 [M+H]⁺.
Example 186	 N-(3-methyloxetan-3-yl)-8-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.57 (s, 1H), 8.76 (s, 1H), 8.13 (s, 1H), 6.79 (s, 1H), 4.63 (d, <i>J</i> = 5.6 Hz, 2H), 4.19 (d, <i>J</i> = 6.2 Hz, 2H), 4.01 - 3.96 (m, 1H), 3.91 - 3.85 (m, 2H), 3.81 - 3.77 (m, 1H), 3.14 - 3.12 (m, 1H), 2.82 - 2.80 (m, 1H), 2.71 - 2.69 (m, 1H), 2.34 - 2.30 (m, 2H), 2.24 - 2.20 (m, 1H), 1.70 - 1.64 (m, 1H), 1.50 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 558 [M+H]⁺.
Example 187	 4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(3-methyloxetan-3-yl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-(2-(dimethylamino)ethyl)-N-methylpiperazine-1-carboxamide	¹H NMR (400 MHz, CD₃OD) δ 9.84 (s, 1H), 7.90 (s, 1H), 7.26 (d, <i>J</i> = 53.5 Hz, 1H), 6.75 (s, 1H), 4.79 (d, <i>J</i> = 6.3 Hz, 2H), 4.32 (d, <i>J</i> = 6.6 Hz, 2H), 3.63 - 3.60 (m, 4H), 3.57 - 3.54 (m, 2H), 3.42 - 3.39 (m, 4H), 3.38 - 3.34 (m, 3H), 3.04 - 3.03 (m, 2H), 2.98 (s, 6H), 1.65 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 614 [M+H]⁺.

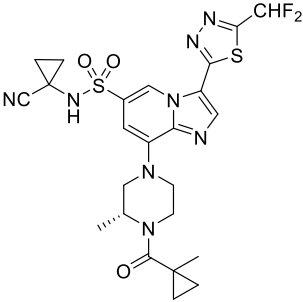
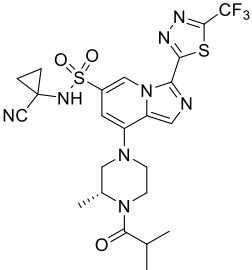
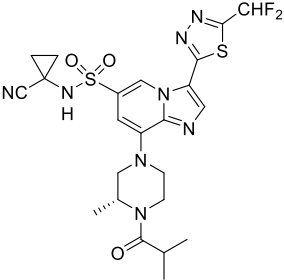
Example 188	 4-(1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(3-methyloxetan-3-yl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-(2-(dimethylamino)ethyl)-N-methylpiperazine-1-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.61 (s, 1H), 8.77 (s, 1H), 7.76 (t, <i>J</i> = 53.2 Hz, 1H), 6.87 (s, 1H), 4.63 (d, <i>J</i> = 6.2 Hz, 2H), 4.19 (d, <i>J</i> = 6.5 Hz, 2H), 3.42 - 3.37 (m, 4H), 3.17 - 3.10 (m, 4H), 2.86 (s, 3H), 2.59 - 2.51 (m, 4H), 2.27 (s, 6H), 1.50 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 648 [M+H]⁺.
Example 189	 8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.91 (d, <i>J</i> = 1.5 Hz, 1H), 8.50 (s, 1H), 7.14 (d, <i>J</i> = 1.5 Hz, 1H), 4.79 (d, <i>J</i> = 6.3 Hz, 2H), 4.32 (d, <i>J</i> = 6.7 Hz, 2H), 3.85 - 3.80 (m, 4H), 3.61 - 3.55 (m, 2H), 1.64 (s, 3H), 1.47 (d, <i>J</i> = 6.5 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 532 [M+H]⁺.
Example 190	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.73 (s, 1H), 8.09 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.75 (s, 1H), 4.63 (d, <i>J</i> = 5.0 Hz, 2H), 4.19 (d, <i>J</i> = 6.3 Hz, 2H), 4.02 - 3.96 (m, 1H), 3.91 - 3.84 (m, 2H), 3.81 - 3.76 (m, 1H), 3.17 - 3.10 (m, 1H), 2.85 - 2.77 (m, 1H), 2.71 - 2.65 (m, 1H), 2.38 - 2.29 (m, 2H), 2.25 - 2.18 (m, 1H), 1.70 - 1.62 (m, 1H), 1.50 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 540 [M+H]⁺.
Example 191		¹H NMR (400 MHz, CD₃OD) δ 9.83 (s, 1H), 7.90 (s, 1H), 7.47 - 7.17 (t, <i>J</i> = 53.6, 1H), 6.81 (s, 1H), 4.79 (d, <i>J</i> = 6.3 Hz, 2H), 4.74 - 4.58 (m, 2H), 4.31 (d, <i>J</i> = 6.3 Hz, 2H), 3.86 - 3.78 (m, 2H), 3.74 - 3.65 (m, 1H), 3.47 - 3.35 (m,

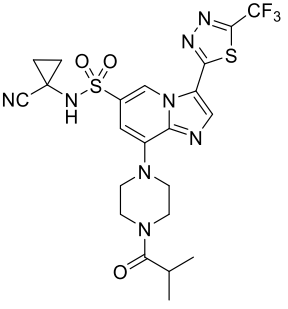
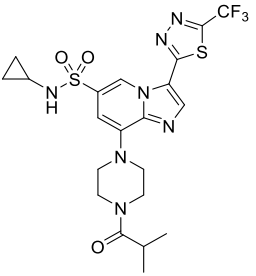
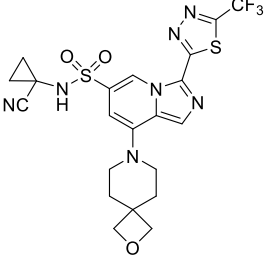
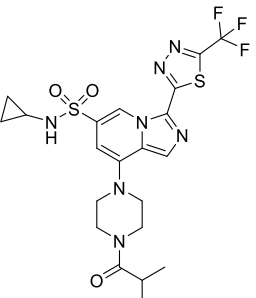
	(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(fluoromethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	2H), 3.19 - 3.04 (m, 2H), 1.64 (s, 3H). LC/MS (ESI) (m/z): 518 [M+H] ⁺ .
Example 192	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 9.99 (s, 1H), 7.75 (s, 1H), 7.07 (t, <i>J</i> = 53.2 Hz, 1H), 6.70 (s, 1H), 5.91 (s, 1H), 4.13 - 3.90 (m, 4H), 3.50 - 3.23 (m, 4H), 3.36 (s, 3H), 1.73 - 1.68 (m, 2H), 1.54 - 1.49 (m, 2H), 1.18 - 1.12 (m, 2H), 1.02 - 0.96 (m, 2H). LC/MS (ESI) (m/z): 579 [M+H] ⁺ .
Example 193	 8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 8.44 (s, 1H), 8.14 (s, 1H), 6.76 (s, 1H), 4.05 - 3.76 (m, 4H), 3.39 - 3.35 (m, 4H), 3.28 (s, 3H), 1.16 (s, 3H), 1.06 - 1.02 (m, 2H), 0.96 - 0.92 (m, 2H), 0.75 - 0.71 (m, 2H), 0.48 - 0.44 (m, 2H). LC/MS (ESI) (m/z): 586 [M+H] ⁺ .
Example 194	 N-cyclopropyl-8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 9.93 (s, 1H), 7.77 (s, 1H), 6.74 (s, 1H), 5.10 (s, 1H), 4.14 - 3.96 (m, 4H), 3.46 - 3.32 (m, 4H), 3.39 (s, 3H), 2.51 - 2.45 (m, 1H), 1.21 - 1.15 (m, 2H), 1.05 - 0.99 (m, 2H), 0.79 - 0.71 (m, 4H). LC/MS (ESI) (m/z): 572 [M+H] ⁺ .

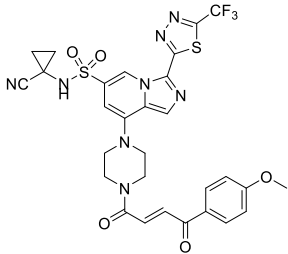
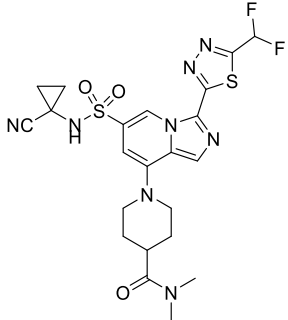
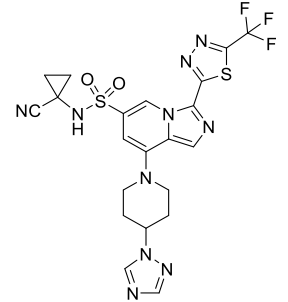
	ifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 195	 N-cyclopropyl-7-fluoro-8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (d, <i>J</i> = 5.1 Hz, 1H), 8.62 (d, <i>J</i> = 2.3 Hz, 1H), 8.05 (s, 1H), 3.97 - 3.70 (m, 4H), 3.44 - 3.40 (m, 4H), 2.46 - 2.41 (m, 1H), 1.05 - 1.00 (m, 2H), 0.95 - 0.91 (m, 2H), 0.57 - 0.52 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 590 [M+H] ⁺ .
Example 196	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.61 (s, 1H), 8.42 (s, 1H), 8.09 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.72 (s, 1H), 4.16 - 3.71 (m, 4H), 3.38 - 3.33 (m, 4H), 3.27 (s, 3H), 1.16 (s, 3H), 1.06 - 1.01 (m, 2H), 0.95 - 0.90 (m, 2H), 0.76 - 0.71 (m, 2H), 0.48 - 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 568 [M+H] ⁺
Example 197	 (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-methoxycyclopropane-1-carbonyl)-3-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.60 (s, 1H), 8.42 (s, 1H), 7.97 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.71 (s, 1H), 5.00 - 4.62 (m, 1H), 4.50 - 4.26 (m, 1H), 3.74 - 3.67 (m, 2H), 3.31 - 3.28 (m, 1H), 3.26 (s, 3H), 3.09 - 3.03 (m, 1H), 3.01 - 2.80 (m, 1H), 1.58 - 1.32 (m, 3H), 1.16 (s, 3H), 1.10 - 0.97 (m, 2H), 0.93 - 0.85 (m, 2H), 0.79 - 0.67 (m, 2H), 0.51 - 0.40 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 582 [M+H] ⁺ .

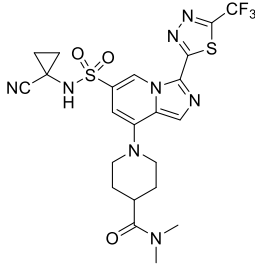
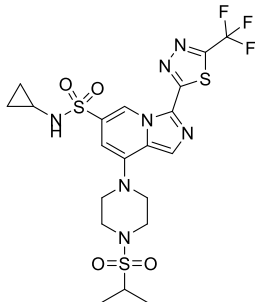
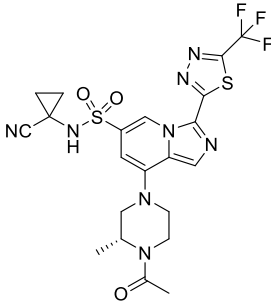
	methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 198	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-7-fluoro-8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.89 (d, <i>J</i> = 5.1 Hz, 1H), 7.89 (s, 1H), 7.33 (t, <i>J</i> = 53.5 Hz, 1H), 4.12 - 3.79 (m, 4H), 3.50 - 3.45 (m, 4H), 3.37 (s, 3H), 1.32 (s, 3H), 1.12 - 1.08 (m, 2H), 1.02 - 0.98 (m, 2H), 0.91 - 0.87 (m, 2H), 0.56 - 0.52 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 586 [M+H] ⁺ .
Example 199	 1-cyano-8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.72 (s, 1H), 8.61 (s, 1H), 7.25 (s, 1H), 4.11 - 3.76 (m, 4H), 3.28 (s, 3H), 3.26 - 3.20 (m, 4H), 1.16 (s, 3H), 1.08 - 1.02 (m, 2H), 0.96 - 0.90 (m, 2H), 0.77 - 0.71 (m, 2H), 0.51 - 0.44 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 611 [M+H] ⁺ .
Example 200	 (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(fluoromethyl)-4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.86 (s, 1H), 7.91 (s, 1H), 7.33 (t, <i>J</i> = 53.6 Hz, 1H), 6.78 (s, 1H), 5.37 - 4.95 (m, 2H), 4.79 - 4.42 (m, 2H), 3.99 (d, <i>J</i> = 13.2 Hz, 1H), 3.74 (d, <i>J</i> = 10.8 Hz, 1H), 3.37 (s, 3H), 3.35 - 3.32 (m, 1H), 3.15 - 2.97 (m, 2H), 1.26 (s, 3H), 1.16 - 1.09 (m, 2H), 1.07 - 0.96 (m, 2H), 0.86 - 0.79 (m, 2H), 0.57 - 0.46 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 600 [M+H] ⁺ .

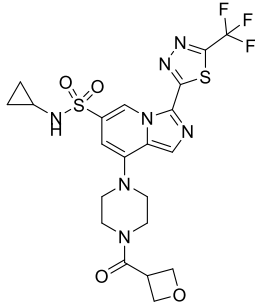
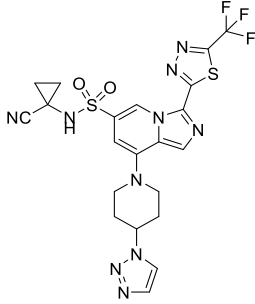
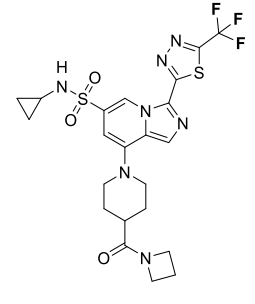
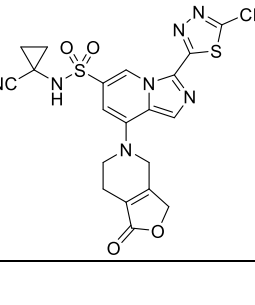
	-a]pyridine-6-sulfonamide	
Example 201	 (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(hydroxymethyl)-4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.83 (s, 1H), 8.20 (s, 1H), 7.33 (t, <i>J</i> = 53.6 Hz, 1H), 6.75 (s, 1H), 4.72 - 4.58 (m, 2H), 4.25 - 4.12 (m, 2H), 3.90 - 3.74 (m, 1H), 3.71 - 3.60 (m, 2H), 3.37 (s, 3H), 3.04 - 2.92 (m, 2H), 1.26 (s, 3H), 1.13 - 1.09 (m, 2H), 1.04 - 0.98 (m, 2H), 0.85 - 0.81 (m, 2H), 0.52 - 0.48 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 598 [M+H] ⁺ .
Example 202	 8-(4-(1-isopropoxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 8.45 (s, 1H), 8.14 (s, 1H), 6.75 (s, 1H), 4.06 - 4.01 (m, 1H), 3.81 - 3.74 (m, 2H), 3.43 - 3.33 (m, 6H), 1.16 (s, 3H), 1.12 (d, <i>J</i> = 6.2 Hz, 6H), 1.05 - 0.99 (m, 2H), 0.97 - 0.89 (m, 2H), 0.75 - 0.72 (m, 2H), 0.48 - 0.44 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 614 [M+H] ⁺ .
Example 203	 8-(4-(1-(methoxy-<i>d</i>₃)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.57 (s, 1H), 8.73 (s, 1H), 8.14 (s, 1H), 6.77 (s, 1H), 4.65 - 4.62 (m, 2H), 4.20 - 4.17 (m, 2H), 4.01 - 3.69 (m, 4H), 3.42 - 3.35 (m, 4H), 1.50 (s, 3H), 1.05 - 1.01 (m, 2H), 0.95 - 0.91 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 605 [M+H] ⁺ .

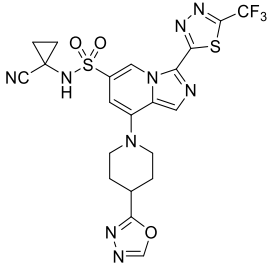
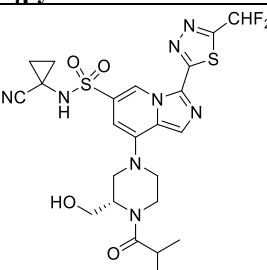
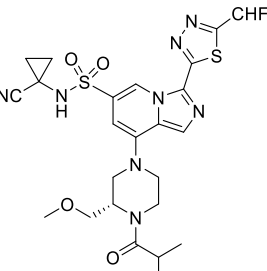
Example 204	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.74 (s, 1H), 9.43 (s, 1H), 8.66 (s, 1H), 7.70 (t, <i>J</i> = 53.0 Hz, 1H), 6.99 (s, 1H), 4.75 - 4.61 (m, 1H), 4.46 - 4.35 (m, 1H), 4.34 - 4.17 (m, 2H), 3.74 - 3.57 (m, 1H), 3.13 - 3.03 (m, 1H), 3.00 - 2.87 (m, 1H), 1.52 - 1.43 (m, 2H), 1.42 - 1.36 (m, 2H), 1.32 (s, 3H), 1.27 (s, 3H), 0.90 - 0.78 (m, 2H), 0.63 - 0.53 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 577 [M+H]⁺.
Example 205	 (R)-N-(1-cyanocyclopropyl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.65 (s, 1H), 9.49 (s, 1H), 8.04 (s, 1H), 6.69 (s, 1H), 4.78 - 4.40 (m, 1H), 3.99 - 3.65 (m, 3H), 3.12 - 2.85 (m, 4H), 1.50 - 1.47 (m, 2H), 1.40 - 1.37 (m, 2H), 1.32 - 1.21 (m, 3H), 1.06 - 1.01 (m, 6H). LC/MS (ESI) (<i>m/z</i>): 583 [M+H]⁺.
Example 206	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.74 (d, <i>J</i> = 1.5 Hz, 1H), 9.45 (s, 1H), 8.67 (s, 1H), 7.71 (t, <i>J</i> = 53.2 Hz, 1H), 6.98 (s, 1H), 4.92 - 4.06 (m, 4H), 4.05 - 3.53 (m, 1H), 3.15 - 3.10 (m, 1H), 3.02 - 2.85 (m, 2H), 1.53 - 1.46 (m, 2H), 1.42 - 1.35 (m, 3H), 1.30 - 1.18 (m, 2H), 1.06 (d, <i>J</i> = 6.6 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 565 [M+H]⁺.

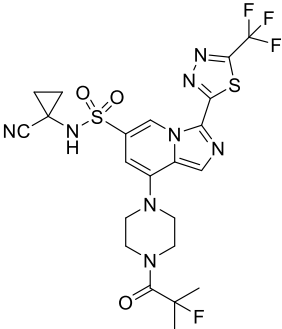
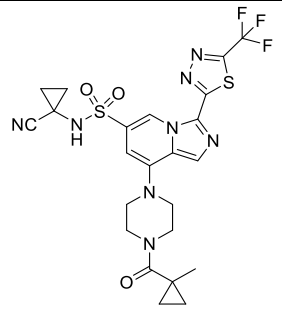
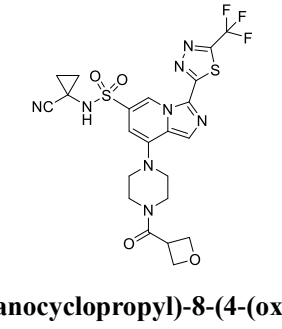
Example 207	 N-(1-cyanocyclopropyl)-8-(4-isobutyryl piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.73 (s, 1H), 9.48 (s, 1H), 8.72 (s, 1H), 7.02 (s, 1H), 3.79 – 3.59 (m, 8H), 3.00 – 2.92 (m, 1H), 1.49 – 1.42 (m, 2H), 1.41 – 1.34 (m, 2H), 1.04 (d, <i>J</i> = 6.1 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 569 [M+H]⁺.
Example 208	 N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (d, <i>J</i> = 1.4 Hz, 1H), 8.70 (s, 1H), 8.25 (s, 1H), 7.04 (d, <i>J</i> = 1.3 Hz, 1H), 3.81 – 3.59 (m, 8H), 3.02 – 2.93 (m, 1H), 2.28 – 2.21 (m, 1H), 1.05 (d, <i>J</i> = 6.7 Hz, 6H), 0.55 – 0.50 (m, 2H), 0.50 – 0.45 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 544 [M+H]⁺.
Example 209	 N-(1-cyanocyclopropyl)-8-(2-oxa-7-azapiro[3.5]nonan-7-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.62 (s, 1H), 9.47 (s, 1H), 8.04 (s, 1H), 6.70 (d, <i>J</i> = 0.9 Hz, 1H), 4.41 (s, 4H), 3.29 – 3.25 (m, 4H), 2.07 – 1.99 (m, 4H), 1.51 – 1.45 (m, 2H), 1.44 – 1.37 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 540 [M+H]⁺.
Example 210	 N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.28 (s, 1H), 8.13 (s, 1H), 6.73 (s, 1H), 3.82 – 3.71 (m, 4H), 3.42 – 3.34 (m, 4H), 2.97 – 2.90 (m, 1H), 2.29 – 2.22 (m, 1H), 1.05 (d, <i>J</i> = 6.3 Hz, 6H), 0.54 – 0.45 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 544 [M+H]⁺.

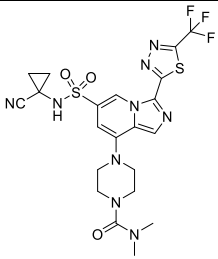
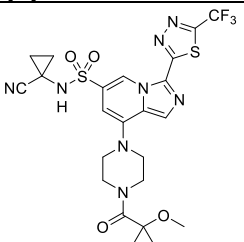
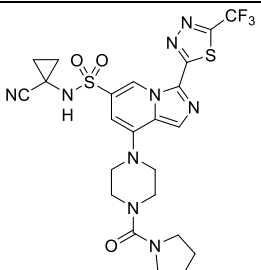
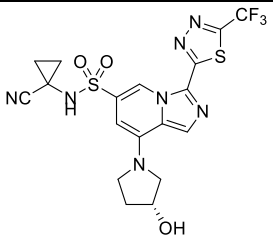
	N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 211	 (E)-N-(1-cyanocyclopropyl)-8-(4-(4-(4-methoxyphenyl)-4-oxobut-2-enoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.66 (s, 1H), 9.50 (s, 1H), 8.16 (s, 1H), 8.07 (d, <i>J</i> = 8.6 Hz, 2H), 7.84 (d, <i>J</i> = 15.1 Hz, 1H), 7.49 (d, <i>J</i> = 15.2 Hz, 1H), 7.11 (d, <i>J</i> = 8.8 Hz, 2H), 6.71 (s, 1H), 3.92 - 3.85 (m, 7H), 3.45 - 3.40 (m, 4H), 1.49 - 1.44 (m, 2H), 1.41 - 1.35 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 687 [M+H] ⁺ .
Example 212	 1-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)-N,N-dimethylpiperidine-4-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (s, 1H), 9.47 (s, 1H), 8.02 (s, 1H), 7.61 (t, <i>J</i> = 53.1 Hz, 1H), 6.66 (s, 1H), 3.86 - 3.78 (m, 2H), 3.09 (s, 3H), 3.05 - 2.98 (m, 2H), 2.95 - 2.88 (m, 1H), 2.85 (s, 3H), 1.87 - 1.76 (m, 4H), 1.51 - 1.46 (m, 2H), 1.41 - 1.35 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 551 [M+H] ⁺ .
Example 213	 8-(4-(1H-1,2,4-triazol-1-yl)piperidin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (s, 1H), 8.64 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 6.76 (s, 1H), 4.69 - 4.60 (m, 1H), 3.93 - 3.86 (m, 2H), 3.20 - 3.13 (m, 2H), 2.30 - 2.22 (m, 4H), 1.52 - 1.46 (m, 2H), 1.42 - 1.36 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 565 [M+H] ⁺ .

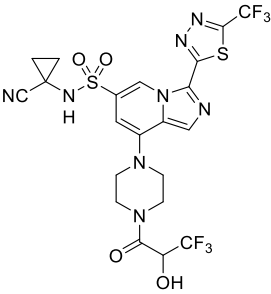
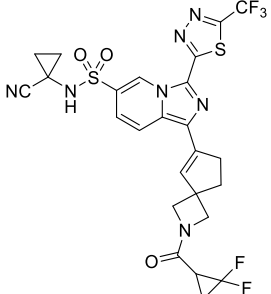
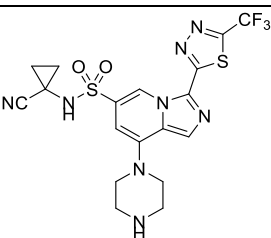
Example 214	 1-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)-N,N-dimethylpiperidine-4-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.63 (s, 1H), 9.50 (s, 1H), 8.07 (s, 1H), 6.69 (s, 1H), 3.85 - 3.78 (m, 2H), 3.09 (s, 3H), 3.04 - 3.00 (m, 2H), 2.96 - 2.91 (m, 1H), 2.85 (s, 3H), 1.88 - 1.81 (m, 4H), 1.51 - 1.45 (m, 2H), 1.41 - 1.36 (m, 2H). LC/MS (ESI) (m/z): 569 [M+H]⁺.
Example 215	 N-cyclopropyl-8-(4-(isopropylsulfonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.61 (s, 1H), 8.29 (d, <i>J</i> = 2.2 Hz, 1H), 8.11 (s, 1H), 6.77 (s, 1H), 3.57 - 3.52 (m, 4H), 3.47 - 3.42 (m, 1H), 3.40 - 3.36 (m, 4H), 2.30 - 2.24 (m, 1H), 1.29 (d, <i>J</i> = 6.8 Hz, 6H), 0.56 - 0.52 (m, 2H), 0.51 - 0.46 (m, 2H). LC/MS (ESI) (m/z): 580 [M+H]⁺.
Example 216	 (R)-8-(4-acetyl-3-methylpiperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 8.03 (s, 1H), 6.69 (s, 1H), 4.37 - 4.26 (m, 1H), 3.84 - 3.73 (m, 3H), 3.16 - 3.02 (m, 3H), 2.08 (d, <i>J</i> = 11.6 Hz, 3H), 1.48 - 1.42 (m, 3H), 1.38 - 1.33 (m, 2H), 1.32 - 1.26 (m, 2H). LC/MS (ESI) (m/z): 555 [M+H]⁺.

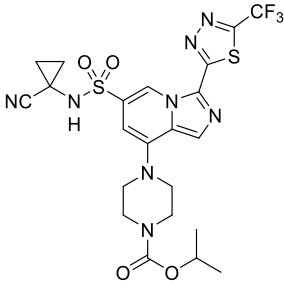
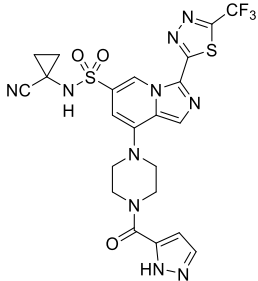
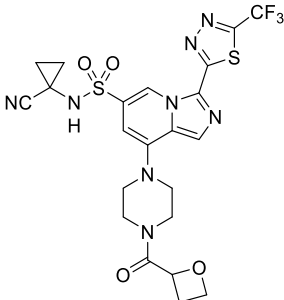
Example 217	 N-cyclopropyl-8-(4-(oxetane-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.29 (s, 1H), 8.12 (s, 1H), 6.72 (s, 1H), 4.79 - 4.65 (m, 4H), 4.29 - 4.15 (m, 1H), 3.83 - 3.74 (m, 2H), 3.47 - 3.43 (m, 2H), 3.33 - 3.22 (m, 4H), 2.29 - 2.23 (m, 1H), 0.57 - 0.51 (m, 2H), 0.50 - 0.43 (m, 2H). LC/MS (ESI) (m/z): 558 [M+H]
Example 218	 8-(4-(1H-1,2,3-triazol-1-yl)piperidin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.53 (s, 1H), 8.29 (s, 1H), 8.12 (s, 1H), 7.79 (s, 1H), 6.78 (s, 1H), 4.97 - 4.82 (m, 1H), 3.93 (d, <i>J</i> = 12.6 Hz, 2H), 3.26 - 3.17 (m, 2H), 2.38 - 2.26 (m, 4H), 1.52 - 1.38 (m, 4H). LC/MS (ESI) (m/z): 565 [M+H]⁺.
Example 219	 8-(4-(azetidine-1-carbonyl)piperidin-1-yl)-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.55 (s, 1H), 8.28 (d, <i>J</i> = 2.5 Hz, 1H), 8.04 (s, 1H), 6.71 (d, <i>J</i> = 0.9 Hz, 1H), 4.22 (t, <i>J</i> = 7.6 Hz, 2H), 3.86 (t, <i>J</i> = 7.7 Hz, 2H), 3.81 - 3.76 (m, 2H), 3.02 - 2.94 (m, 2H), 2.27 - 2.20 (m, 3H), 1.84 - 1.77 (m, 4H), 0.89 - 0.81 (m, 1H), 0.54 - 0.47 (m, 4H). LC/MS (ESI) (m/z): 556 [M+H]⁺
Example 220	 8-(4-(1H-1,2,3-triazol-1-yl)piperidin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 8.15 (s, 1H), 6.75 (s, 1H), 5.00 (s, 2H), 4.32 (s, 2H), 3.71 - 3.64 (m, 2H), 2.57 - 2.53 (m, 2H), 1.48 - 1.43 (m, 2H), 1.40 - 1.34 (m, 2H). LC/MS (ESI) (m/z): 552 [M+H]⁺.

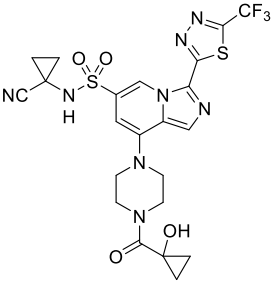
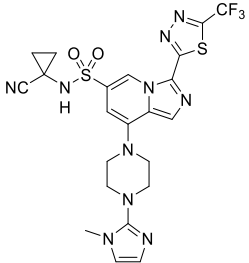
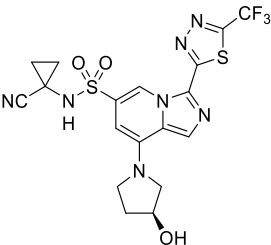
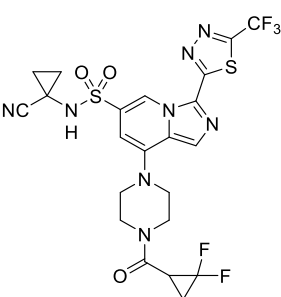
	N-(1-cyanocyclopropyl)-8-(1-oxo-1,4,6,7-tetrahydrofuro[3,4-c]pyridin-5(3H)-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide e	
Example 221	 8-(4-(1,3,4-oxadiazol-2-yl)piperidin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 9.50 (s, 1H), 9.21 (s, 1H), 8.10 (s, 1H), 6.74 (s, 1H), 3.85 – 3.75 (m, 2H), 3.40 – 3.34 (m, 1H), 3.20 – 3.12 (m, 2H), 2.27 – 2.21 (m, 2H), 2.09 – 2.01 (m, 2H), 1.51 – 1.45 (m, 2H), 1.42 – 1.36 (m, 2H). LC/MS (ESI) (m/z): 566 [M+H]⁺.
Example 222	 (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(hydroxymethyl)-4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.68 (s, 1H), 9.48 (s, 1H), 8.30 - 8.10 (m, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.69 (s, 1H), 5.36 - 5.18 (m, 1H), 4.58 - 4.36 (m, 1H), 4.19 - 4.10 (m, 1H), 4.04 - 3.87 (m, 2H), 3.61 - 3.55 (m, 2H), 3.05 - 2.82 (m, 4H), 1.53 - 1.44 (m, 2H), 1.40 - 1.32 (m, 2H), 1.10 - 1.00 (m, 6H). LC/MS (ESI) (m/z): 581 [M+H]⁺.
Example 223	 (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-(methoxymethyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.72 (s, 1H), 9.52 (s, 1H), 8.05 (s, 1H), 7.72 (t, <i>J</i> = 53.2 Hz, 1H), 6.73 (s, 1H), 4.80 - 4.40 (m, 1H), 4.08 - 4.00 (m, 1H), 3.95 - 3.90 (m, 1H), 3.69 - 3.52 (m, 2H), 3.42 (s, 3H), 3.31 - 2.95 (m, 4H), 2.94 - 2.88 (m, 1H), 1.54 - 1.49 (m, 2H), 1.45 - 1.38 (m, 2H), 1.11 - 1.05 (m, 6H). LC/MS (ESI) (m/z): 595 [M+H]⁺.

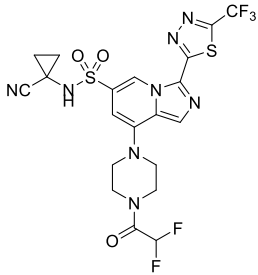
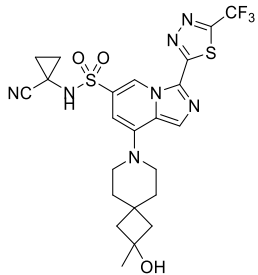
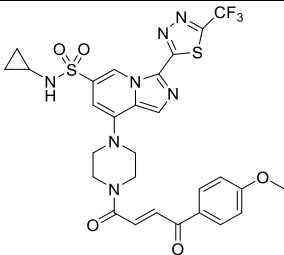
Example 224	 N-(1-cyanocyclopropyl)-8-(4-(2-fluoro-2-methylpropanoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 8.16 (s, 1H), 6.72 (s, 1H), 4.02 – 3.77 (m, 4H), 3.50 – 3.42 (m, 4H), 1.63 (s, 3H), 1.58 (s, 3H), 1.50 – 1.46 (m, 2H), 1.41 – 1.37 (m, 2H). LC/MS (ESI) (m/z): 587 [M+H]⁺.
Example 225	 N-(1-cyanocyclopropyl)-8-(4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 9.50 (s, 1H), 8.15 (s, 1H), 6.73 (s, 1H), 3.90 – 3.71 (m, 4H), 3.42 – 3.37 (m, 4H), 1.52 – 1.46 (m, 2H), 1.42 – 1.34 (m, 2H), 1.29 (s, 3H), 0.88 – 0.84 (m, 2H), 0.62 – 0.53 (m, 2H). LC/MS (ESI) (m/z): 581 [M+H]⁺.
Example 226	 N-(1-cyanocyclopropyl)-8-(4-(oxetane-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 9.51 (s, 1H), 8.13 (s, 1H), 6.70 (s, 1H), 4.80 – 4.67 (m, 4H), 4.26 – 4.15 (m, 1H), 3.80 – 3.71 (m, 2H), 3.48 – 3.43 (m, 2H), 3.39 – 3.35 (m, 2H), 3.32 – 3.26 (m, 2H), 1.51 – 1.44 (m, 2H), 1.43 – 1.36 (m, 2H). LC/MS (ESI) (m/z): 583 [M+H]⁺.

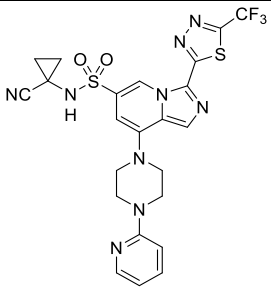
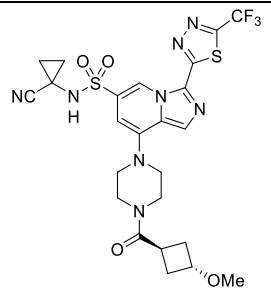
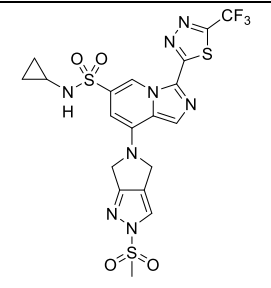
Example 227	 4-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)-N,N-dimethylpiperazine-1-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.65 (s, 1H), 9.48 (s, 1H), 8.12 (d, <i>J</i> = 1.8 Hz, 1H), 6.72 (s, 1H), 3.39 - 3.37 (m, 4H), 3.33 - 3.18 (m, 4H), 2.80 (s, 6H), 1.52 - 1.45 (m, 2H), 1.42 - 1.36 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 570 [M+H]⁺.
Example 228	 N-(1-cyanocyclopropyl)-8-(4-(1-methoxycyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 8.17 (s, 1H), 6.74 (s, 1H), 4.05 - 3.73 (m, 4H), 3.41 - 3.39 (m, 4H), 3.27 (s, 3H), 1.50 - 1.45 (m, 2H), 1.41 - 1.36 (m, 2H), 1.06 - 1.01 (m, 2H), 0.96 - 0.91 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 597 [M+H]⁺.
Example 229	 N-(1-cyanocyclopropyl)-8-(4-(pyrrolidin-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.65 (s, 1H), 9.54 (s, 1H), 8.14 (s, 1H), 6.71 (s, 1H), 3.47 - 3.42 (m, 4H), 3.37 - 3.33 (m, 8H), 1.81 - 1.75 (m, 4H), 1.50 - 1.45 (m, 2H), 1.41 - 1.36 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 596 [M+H]⁺.
Example 230	 (R)-N-(1-cyanocyclopropyl)-8-(3-hydroxypyrrolidin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.41 (s, 1H), 8.26 (s, 1H), 6.14 (s, 1H), 5.24 - 5.06 (m, 1H), 4.50 (s, 1H), 3.92 - 3.67 (m, 3H), 3.55 - 3.50 (m, 1H), 2.15 - 2.08 (m, 1H), 2.05 - 2.00 (m, 1H), 1.49 - 1.43 (m, 2H), 1.39 - 1.34 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 500 [M+H]⁺.

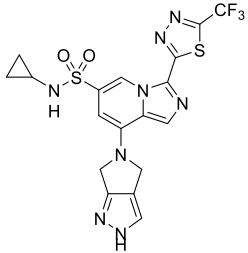
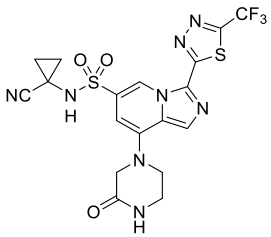
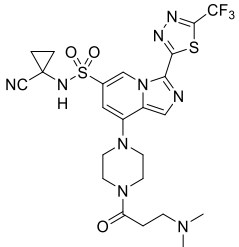
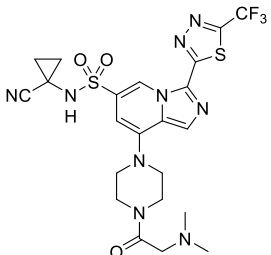
	1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 231	 N-(1-cyanocyclopropyl)-8-(4-(3,3,3-trifluoro-2-hydroxypropanoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.64 (s, 1H), 8.15 (s, 1H), 6.86 (d, <i>J</i> = 8.6 Hz, 1H), 6.70 (s, 1H), 5.23 - 5.14 (m, 1H), 3.88 - 3.73 (m, 4H), 3.40 - 3.37 (m, 4H), 1.48 - 1.43 (m, 2H), 1.39 - 1.34 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 625 [M+H] ⁺ .
Example 232	 N-(1-cyanocyclopropyl)-1-(2-(2,2-difluorocyclopropane-1-carbonyl)-2-azaspiro[3.4]oct-5-en-6-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.45 - 8.38 (m, 1H), 7.48 - 7.44 (m, 1H), 6.74 (d, <i>J</i> = 3.2 Hz, 1H), 4.44 - 4.26 (m, 2H), 4.09 - 4.05 (m, 1H), 3.99 - 3.95 (m, 1H), 3.01 - 2.97 (m, 2H), 2.36 - 2.32 (m, 2H), 1.92 - 1.89 (m, 1H), 1.47 - 1.43 (m, 2H), 1.35 - 1.32 (m, 2H), 1.29 - 1.21 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 626 [M+H] ⁺ .
Example 233	 N-(1-cyanocyclopropyl)-8-(piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.74 (s, 1H), 8.22 (s, 1H), 6.82 (s, 1H), 3.51 (s, 4H), 3.33 (s, 4H), 1.57 - 1.53 (m, 2H), 1.49 - 1.45 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 499 [M+H] ⁺ .

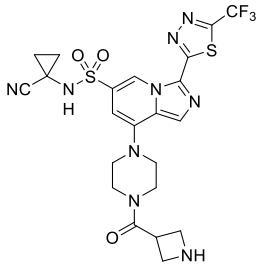
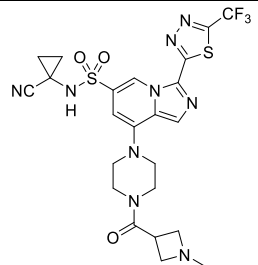
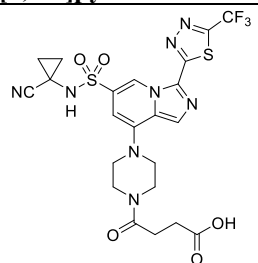
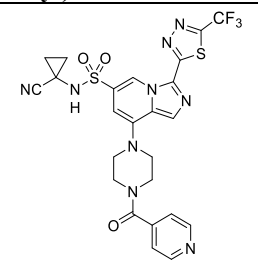
Example 234	 isopropyl 4-(6-(N-(1-cyanocyclopropyl)sulfamoyl) -3-(5-(trifluoromethyl)-1,3,4-thiadiazol- 2-yl)imidazo[1,5-a]pyridin-8-yl)piperazi ne-1-carboxylate	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.50 (s, 1H), 8.11 (s, 1H), 6.71 (s, 1H), 4.87 - 4.81 (m, 1H), 3.66 - 3.62 (m, 4H), 3.36 - 3.35 (m, 4H), 1.51 - 1.47 (m, 2H), 1.41 - 1.38 (m, 2H), 1.23 (d, <i>J</i> = 6.2 Hz, 6H). LC/MS (ESI) (m/z): 585 [M+H]⁺.
Example 235	 8-(4-(1H-pyrazole-5-carbonyl)piperazin -1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifl uoromethyl)-1,3,4-thiadiazol-2-yl)imida zo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 9.49 (s, 1H), 8.17 (s, 1H), 7.83 (s, 1H), 6.74 (s, 1H), 6.65 (d, <i>J</i> = 2.3 Hz, 1H), 4.28 - 4.19 (m, 2H), 3.95 - 3.88 (m, 2H), 3.50 - 3.45 (m, 4H), 1.50 - 1.46 (m, 2H), 1.42 - 1.38 (m, 2H). LC/MS (ESI) (m/z): 593 [M+H]⁺.
Example 236	 N-(1-cyanocyclopropyl)-8-(4-(oxetane-2- carbonyl)piperazin-1-yl)-3-(5-(trifluoro methyl)-1,3,4-thiadiazol-2-yl)imidazo[1, 5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.50 (s, 1H), 8.15 (s, 1H), 6.71 (s, 1H), 5.55 - 5.43 (m, 1H), 4.62 - 4.54 (m, 1H), 4.47 - 4.38 (m, 1H), 3.80 - 3.71 (m, 2H), 3.60 - 3.51 (m, 2H), 3.43 - 3.36 (m, 4H), 2.91 - 2.76 (m, 2H), 1.52 - 1.45 (m, 2H), 1.42 - 1.33 (m, 2H). LC/MS (ESI) (m/z): 583 [M+H]⁺.

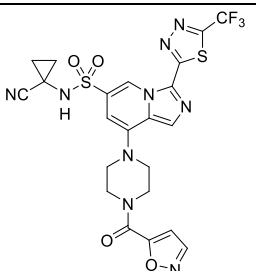
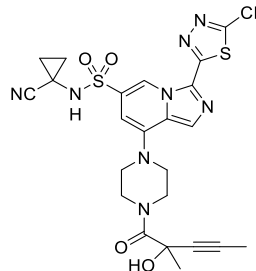
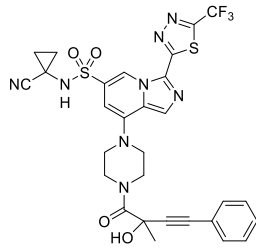
Example 237	 N-(1-cyanocyclopropyl)-8-(4-(1-hydroxycyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 8.16 (s, 1H), 6.73 (s, 1H), 6.44 (s, 1H), 4.13 – 3.72 (m, 4H), 3.38 – 3.35 (m, 4H), 1.52 – 1.44 (m, 2H), 1.41 – 1.33 (m, 2H), 1.02 – 0.95 (m, 2H), 0.84 – 0.78 (m, 2H). LC/MS (ESI) (m/z): 583 [M+H]⁺.
Example 238	 N-(1-cyanocyclopropyl)-8-(4-(1-methyl-1H-imidazol-2-yl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.70 (s, 1H), 9.54 (s, 1H), 8.16 (s, 1H), 7.36 (d, <i>J</i> = 11.2 Hz, 2H), 6.79 (s, 1H), 3.68 (s, 3H), 3.57 – 3.52 (m, 8H), 1.53 – 1.47 (m, 2H), 1.44 – 1.39 (m, 2H). LC/MS (ESI) (m/z): 579 [M+H]⁺.
Example 239	 (S)-N-(1-cyanocyclopropyl)-8-(3-hydroxypyrrolidin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.41 (s, 1H), 9.40 (s, 1H), 8.26 (s, 1H), 6.14 (s, 1H), 5.17 (s, 1H), 3.93 – 3.70 (m, 4H), 3.55 – 3.51 (m, 1H), 2.05 – 2.00 (m, 2H), 1.50 – 1.45 (m, 2H), 1.38 – 1.34 (m, 2H). LC/MS (ESI) (m/z): 500 [M+H]⁺.
Example 240	 N-(1-cyanocyclopropyl)-8-(4-(1,1-difluoroethyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 9.51 (s, 1H), 8.18 (s, 1H), 6.73 (s, 1H), 3.97 – 3.75 (m, 4H), 3.48 – 3.36 (m, 4H), 3.29 – 3.23 (m, 1H), 2.00 – 1.87 (m, 2H), 1.52 – 1.46 (m, 2H), 1.43 – 1.36 (m, 2H). LC/MS (ESI) (m/z): 603 [M+H]⁺.

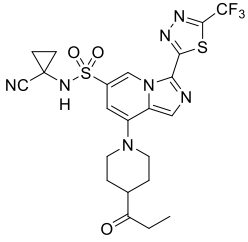
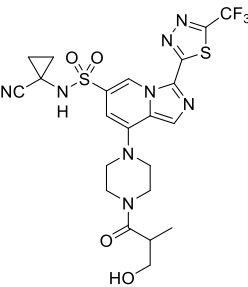
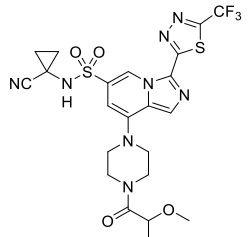
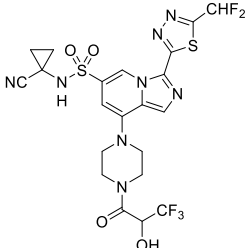
	N-(1-cyanocyclopropyl)-8-(4-(2,2-difluorocyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 241	 N-(1-cyanocyclopropyl)-8-(4-(2,2-difluoroacetyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.68 (s, 1H), 9.51 (s, 1H), 8.18 (s, 1H), 6.97 – 6.69 (m, 2H), 3.84 – 3.77 (m, 4H), 3.45 – 3.38 (m, 4H), 1.53 – 1.46 (m, 2H), 1.43 – 1.35 (m, 2H). LC/MS (ESI) (m/z): 577 [M+H] ⁺ .
Example 242	 N-(1-cyanocyclopropyl)-8-(2-hydroxy-2-methyl-7-azaspiro[3.5]nonan-7-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.60 (s, 1H), 8.01 (s, 1H), 6.68 (d, <i>J</i> = 0.9 Hz, 1H), 4.81 (s, 1H), 3.25 (d, <i>J</i> = 1.0 Hz, 4H), 1.97 – 1.87 (m, 4H), 1.86 – 1.80 (m, 2H), 1.78 – 1.71 (m, 2H), 1.49 – 1.42 (m, 2H), 1.39 – 1.33 (m, 2H), 1.28 (s, 3H). LC/MS (ESI) (m/z): 568 [M+H] ⁺ .
Example 243	 (E)-N-cyclopropyl-8-(4-(4-(4-methoxyphenyl)-4-oxobut-2-enoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.60 (s, 1H), 8.30 (d, <i>J</i> = 2.5 Hz, 1H), 8.14 (s, 1H), 8.07 (d, <i>J</i> = 8.9 Hz, 2H), 7.84 (d, <i>J</i> = 15.2 Hz, 1H), 7.49 (d, <i>J</i> = 15.2 Hz, 1H), 7.11 (d, <i>J</i> = 8.9 Hz, 2H), 6.73 (s, 1H), 3.91 – 3.85 (m, 7H), 3.44 – 3.38 (m, 4H), 2.29 – 2.23 (m, 1H), 0.56 – 0.51 (m, 2H), 0.50 – 0.46 (m, 2H). LC/MS (ESI) (m/z): 662 [M+H] ⁺ .

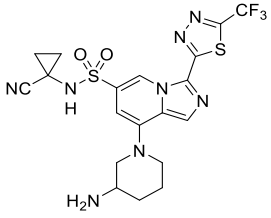
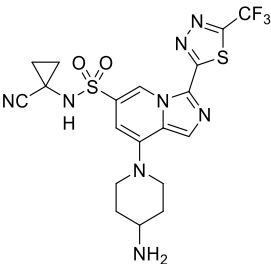
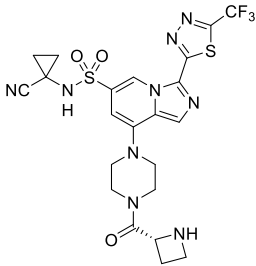
Example 244	 N-(1-cyanocyclopropyl)-8-(4-(pyridin-2-yl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.51 (s, 1H), 8.18 - 8.13 (m, 2H), 7.63 - 7.57 (m, 1H), 6.93 (d, <i>J</i> = 8.6 Hz, 1H), 6.75 (s, 1H), 6.71 (dd, <i>J</i> = 6.8, 4.9 Hz, 1H), 3.80 – 3.75 (m, 4H), 3.50 – 3.46 (m, 4H), 1.49 - 1.38 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 576 [M+H]⁺
Example 245	 N-(1-cyanocyclopropyl)-8-(((1R,3R)-3-methoxycyclobutane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 8.14 (s, 1H), 6.71 (s, 1H), 3.89 – 3.84 (m, 1H), 3.77 – 3.72 (m, 2H), 3.62 – 3.58 (m, 2H), 3.39 – 3.36 (m, 4H), 3.14 (s, 3H), 2.56 – 2.54 (m, 1H), 2.46 – 2.40 (m, 2H), 2.19 – 2.10 (m, 2H), 1.52 – 1.46 (m, 2H), 1.41 – 1.33 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 611 [M+H]⁺.
Example 246	 N-cyclopropyl-8-(2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.47 (s, 1H), 8.43 (s, 1H), 8.26 (s, 1H), 8.23 (s, 1H), 6.37 (s, 1H), 5.02 (s, 2H), 4.89 (s, 2H), 3.60 (s, 3H), 2.31 – 2.28 (m, 1H), 0.56 – 0.51 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 575 [M+H]⁺.

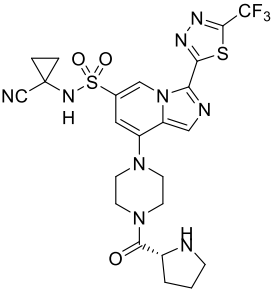
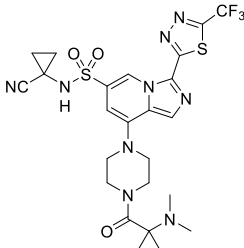
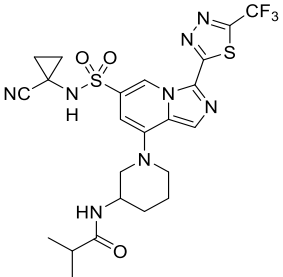
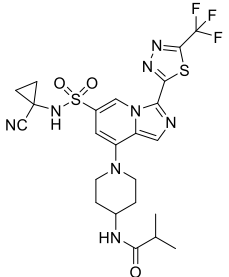
Example 247	 N-cyclopropyl-8-(2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 12.85 (s, 1H), 9.43 (s, 1H), 8.42 (s, 1H), 8.23 (s, 1H), 7.68 (s, 1H), 6.31 (s, 1H), 4.87 – 4.84 (m, 4H), 2.31 – 2.26 (m, 1H), 0.56 – 0.47 (m, 4H). LC/MS (ESI) (m/z): 497 [M+H]⁺.
Example 248	 N-(1-cyanocyclopropyl)-8-(3-oxopiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (s, 1H), 9.48 (s, 1H), 8.20 (s, 1H), 8.17 (s, 1H), 6.65 (s, 1H), 3.94 (s, 2H), 3.72 – 3.65 (m, 2H), 3.49 – 3.42 (m, 2H), 1.49 – 1.45 (m, 2H), 1.41 – 1.36 (m, 2H). LC/MS (ESI) (m/z): 513 [M+H]⁺.
Example 249	 N-(1-cyanocyclopropyl)-8-(4-(3-(dimethylamino)propanoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 9.53 (s, 1H), 9.12 (s, 1H), 8.17 (s, 1H), 6.72 (s, 1H), 3.79 – 3.73 (m, 4H), 3.38 – 3.31 (m, 6H), 2.94 – 2.89 (m, 2H), 2.81 (d, <i>J</i> = 4.8 Hz, 6H), 1.52 – 1.47 (m, 2H), 1.43 – 1.38 (m, 2H). LC/MS (ESI) (m/z): 598 [M+H]⁺.
Example 250	 N-(1-cyanocyclopropyl)-8-(4-(dimethylglycyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 8.16 (s, 1H), 6.72 (s, 1H), 3.83 – 3.72 (m, 4H), 3.45 – 3.36 (m, 6H), 2.35 (s, 6H), 1.51 – 1.44 (m, 2H), 1.43 – 1.36 (m, 2H). LC/MS (ESI) (m/z): 584 [M+H]⁺.

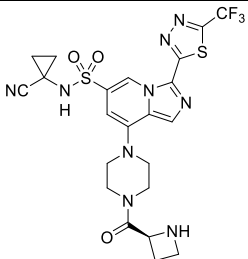
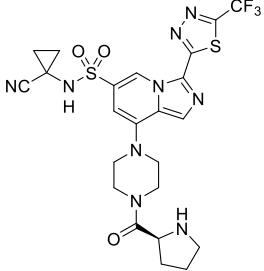
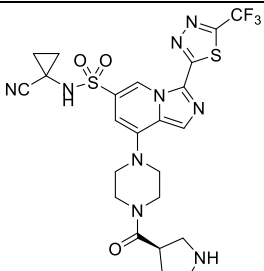
	pyridine-6-sulfonamide	
Example 251	 8-(4-(azetidine-3-carbonyl)piperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.60 (s, 1H), 8.08 (s, 1H), 6.71 (s, 1H), 3.99 - 3.88 (m, 6H), 3.76 - 3.73 (m, 3H), 3.55 - 3.46 (m, 5H), 1.33 - 1.29 (m, 2H), 1.25 - 1.22 (m, 2H). LC/MS (ESI) (m/z): 582 [M+H] ⁺
Example 252	 N-(1-cyanocyclopropyl)-8-(4-(1-methylazetidine-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (s, 1H), 8.19 - 8.15 (m, 1H), 6.70 (s, 1H), 3.75 - 3.71 (m, 2H), 3.58 - 3.50 (m, 6H), 3.34 - 3.30 (m, 4H), 3.29 - 3.27 (m, 1H), 2.27 (s, 3H), 1.49 - 1.43 (m, 2H), 1.39 - 1.33 (m, 2H). LC/MS (ESI) (m/z): 596 [M+H] ⁺ .
Example 253	 4-(4-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperazin-1-yl)-4-oxobutanoic acid	¹ H NMR (400 MHz, CDCl ₃) δ 9.97 (s, 1H), 7.74 (s, 1H), 6.77 (s, 1H), 3.96 - 3.77 (m, 4H), 3.43 - 3.28 (m, 4H), 2.78 - 2.72 (m, 4H), 1.71 - 1.65 (m, 2H), 1.51 - 1.46 (m, 2H). LC/MS (ESI) (m/z): 599 [M+H] ⁺ .
Example 254	 N-(1-cyanocyclopropyl)-8-(4-isonicotinoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.66 (s, 1H), 9.51 (s, 1H), 8.73 - 8.70 (m, 2H), 8.13 (s, 1H), 7.50 - 7.47 (m, 2H), 6.73 (s, 1H), 3.97 - 3.88 (m, 2H), 3.59 - 3.52 (m, 2H), 3.50 - 3.44 (m, 2H), 3.40 - 3.35 (m, 2H), 1.51 - 1.46 (m, 2H), 1.41 - 1.36 (m, 2H). LC/MS (ESI) (m/z): 604

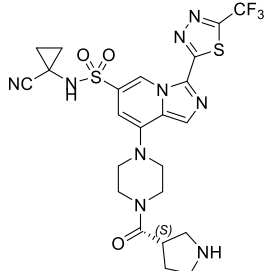
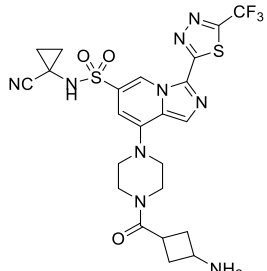
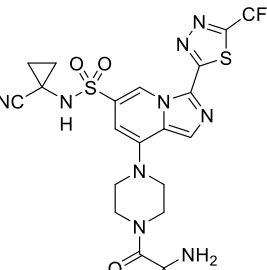
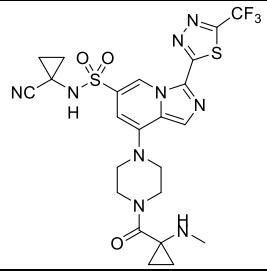
	ylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	$[M+H]^+$.
Example 255	 N-(1-cyanocyclopropyl)-8-(4-(isoxazole-5-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ 9.67 (s, 1H), 9.51 (s, 1H), 8.80 (d, J = 1.9 Hz, 1H), 8.16 (s, 1H), 7.03 (d, J = 1.9 Hz, 1H), 6.73 (d, J = 0.9 Hz, 1H), 3.95 – 3.80 (m, 4H), 3.50 - 3.43 (m, 4H), 1.51 - 1.45 (m, 2H), 1.42 - 1.36 (m, 2H). LC/MS (ESI) (m/z): 594 $[M+H]^+$.
Example 256	 N-(1-cyanocyclopropyl)-8-(4-(2-hydroxy-2-methylpent-3-ynoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ 9.65 (s, 1H), 9.49 (s, 1H), 8.17 (s, 1H), 6.72 (s, 1H), 6.10 (s, 1H), 4.33 – 4.05 (m, 2H), 4.03 – 3.65 (m, 2H), 3.42 – 3.36 (m, 4H), 1.84 (s, 3H), 1.55 (s, 3H), 1.49 – 1.44 (m, 2H), 1.41 – 1.34 (m, 2H). LC/MS (ESI) (m/z): 609 $[M+H]^+$.
Example 257	 N-(1-cyanocyclopropyl)-8-(4-(2-hydroxy-2-methyl-4-phenylbut-3-ynoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO- d_6) δ 9.66 (s, 1H), 9.48 (s, 1H), 8.18 (s, 1H), 7.48 – 7.45 (m, 2H), 7.41 – 7.37 (m, 3H), 6.72 (s, 1H), 6.43 (s, 1H), 4.34 – 4.22 (m, 2H), 3.85 – 3.74 (m, 2H), 3.59 – 3.49 (m, 4H), 1.69 (s, 3H), 1.49 – 1.45 (m, 2H), 1.40 – 1.34 (m, 2H). LC/MS (ESI) (m/z): 671 $[M+H]^+$.

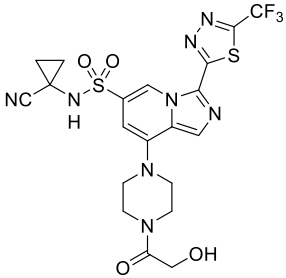
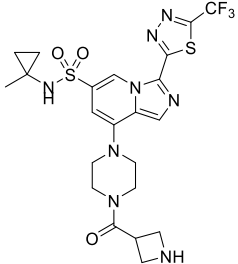
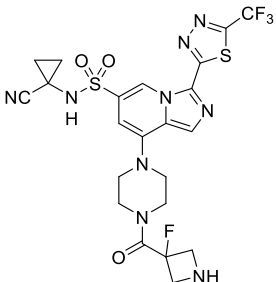
Example 258	 N-(1-cyanocyclopropyl)-8-(4-propionylpiperidin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.94 (s, 1H), 7.73 (s, 1H), 6.69 (s, 1H), 5.65 (s, 1H), 3.86 – 3.80 (m, 2H), 3.06 – 2.98 (m, 2H), 2.58 – 2.53 (m, 3H), 2.10 – 1.92 (m, 4H), 1.72 – 1.69 (m, 2H), 1.53 – 1.50 (m, 2H), 1.12 – 1.08 (m, 3H). LC/MS (ESI) (m/z): 554 [M+H]⁺.
Example 259	 N-(1-cyanocyclopropyl)-8-(4-(3-hydroxy-2-methylpropanoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.99 (s, 1H), 7.75 (s, 1H), 6.74 (s, 1H), 6.20 (s, 1H), 4.04 – 3.94 (m, 1H), 3.86 – 3.76 (m, 4H), 3.43 – 3.32 (m, 4H), 3.06 – 2.81 (m, 2H), 1.73 – 1.69 (m, 2H), 1.53 – 1.50 (m, 2H), 1.19 (d, <i>J</i> = 7.1 Hz, 3H). LC/MS (ESI) (m/z): 585 [M+H]⁺.
Example 260	 N-(1-cyanocyclopropyl)-8-(4-(2-methoxypropanoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 10.00 (s, 1H), 7.75 (s, 1H), 6.83 (s, 1H), 6.52 (s, 1H), 4.26 – 4.19 (m, 1H), 3.98 – 3.92 (m, 4H), 3.44 – 3.34 (m, 7H), 1.73 – 1.68 (m, 2H), 1.52 – 1.48 (m, 2H), 1.46 – 1.45 (m, 3H). LC/MS (ESI) (m/z): 585 [M+H]⁺.
Example 261	 N-(1-cyanocyclopropyl)-3-(5-(difluoroethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(3,3,3-trifluoro-2-hydroxypropionyl)piperidin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.69 (s, 1H), 9.49 (s, 1H), 8.13 (s, 1H), 7.69 (t, <i>J</i> = 53.2 Hz, 1H), 6.87 (d, <i>J</i> = 8.6 Hz, 1H), 6.69 (d, <i>J</i> = 0.8 Hz, 1H), 5.26 – 5.14 (m, 1H), 3.92 – 3.74 (m, 4H), 3.42 – 3.36 (m, 4H), 1.50 – 1.37 (m, 4H). LC/MS (ESI) (m/z): 607 [M+H]⁺.

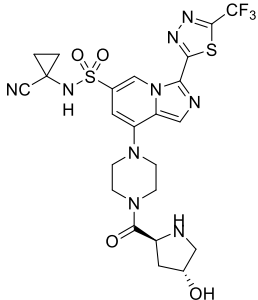
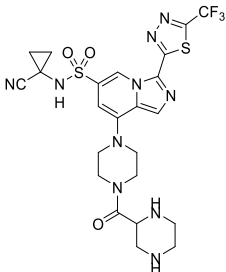
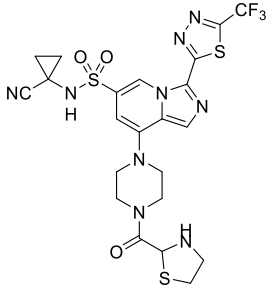
	trifluoro-2-hydroxypropanoyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 262	 8-(3-aminopiperidin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 9.85 (s, 1H), 7.71 (s, 1H), 6.81 (s, 1H), 3.86 – 3.76 (m, 2H), 3.68 – 3.59 (m, 1H), 3.42 – 3.26 (m, 2H), 3.24 – 3.14 (m, 2H), 2.22 – 2.14 (m, 1H), 2.00 – 1.92 (m, 1H), 1.83 – 1.72 (m, 2H), 1.68 – 1.59 (m, 2H), 1.43 – 1.35 (m, 2H). LC/MS (ESI) (m/z): 513 [M+H].
Example 263	 8-(4-aminopiperidin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.55 (s, 1H), 7.99 (s, 1H), 6.71 (s, 1H), 3.80 – 3.74 (m, 2H), 3.62 – 3.58 (m, 1H), 3.18 – 3.15 (m, 2H), 3.03 – 2.96 (m, 2H), 2.05 – 1.98 (m, 2H), 1.78 – 1.70 (m, 2H), 1.30 – 1.24 (m, 2H), 1.21 – 1.14 (m, 2H). LC/MS (ESI) (m/z): 513 [M+H].
Example 264	 (R)-8-(4-(azetidine-2-carbonyl)piperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 9.97 (s, 1H), 7.69 (s, 1H), 6.80 (s, 1H), 5.37 – 5.23 (m, 1H), 4.17 (d, <i>J</i> = 12.8 Hz, 1H), 4.02 – 3.84 (m, 2H), 3.69 – 3.59 (m, 2H), 3.55 – 3.46 (m, 2H), 3.41 – 3.34 (m, 1H), 3.31 – 3.16 (m, 2H), 3.00 – 2.92 (m, 1H), 2.50 – 2.46 (m, 2H), 1.73 – 1.64 (m, 2H), 1.52 – 1.45 (m, 2H). LC/MS (ESI) (m/z): 582 [M+H] ⁺ .

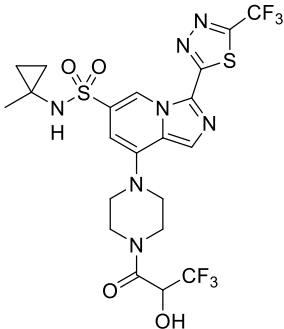
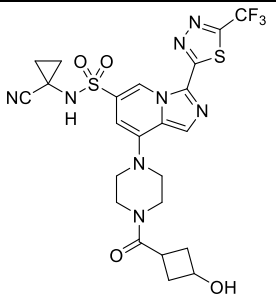
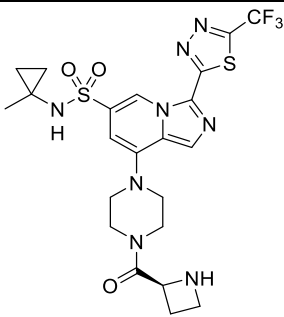
Example 265	 (R)-N-(1-cyanocyclopropyl)-8-(4-propylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.95 (s, 1H), 7.66 (s, 1H), 6.85 (s, 1H), 5.02 - 4.82 (m, 1H), 4.29 (d, <i>J</i> = 12.1 Hz, 1H), 3.96 (d, <i>J</i> = 13.1 Hz, 1H), 3.66 - 3.33 (m, 8H), 2.52 - 2.45 (m, 1H), 2.22 - 1.79 (m, 4H), 1.70 - 1.59 (m, 2H), 1.48 - 1.40 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 596 [M+H]⁺.
Example 266	 N-(1-cyanocyclopropyl)-8-(4-(1-(dimethylamino)cyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.98 (s, 1H), 7.76 (s, 1H), 6.76 (d, <i>J</i> = 0.9 Hz, 1H), 6.43 (s, 1H), 4.01 - 3.93 (m, 4H), 3.41 - 3.35 (m, 4H), 2.33 (s, 6H), 1.72 - 1.68 (m, 2H), 1.52 - 1.47 (m, 2H), 1.09 - 1.00 (m, 2H), 0.97 - 0.91 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 610 [M+H]⁺.
Example 267	 N-(1-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperidin-3-yl)isobutyramide	¹H NMR (400 MHz, CDCl₃) δ 9.91 (s, 1H), 7.83 (s, 1H), 7.00 (s, 1H), 6.63 (s, 1H), 5.75 - 5.67 (m, 1H), 4.41 - 4.31 (m, 1H), 3.85 - 3.73 (m, 2H), 3.39 - 3.31 (m, 1H), 3.12 - 3.05 (m, 1H), 2.46 - 2.37 (m, 1H), 2.05 - 1.97 (m, 1H), 1.90 - 1.83 (m, 1H), 1.81 - 1.72 (m, 2H), 1.71 - 1.63 (m, 2H), 1.49 - 1.40 (m, 2H), 1.20 - 1.14 (m, 6H). LC/MS (ESI) (<i>m/z</i>): 583 [M+H].
Example 268	 N-(1-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperidin-3-yl)isobutyramide	¹H NMR (400 MHz, MeOD) δ 9.85 (s, 1H), 7.87 (s, 1H), 6.79 (s, 1H), 3.99 - 3.89 (m, 1H), 3.86 - 3.79 (m, 2H), 3.15 - 3.06 (m, 2H), 2.52 - 2.43 (m, 1H), 2.12 - 2.04 (m, 2H), 1.85 - 1.75 (m, 2H), 1.57 - 1.52 (m, 2H), 1.47 - 1.42

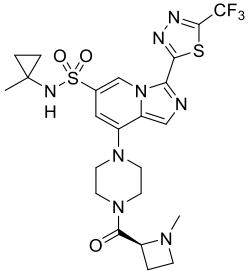
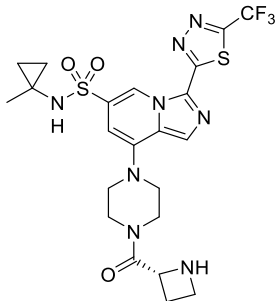
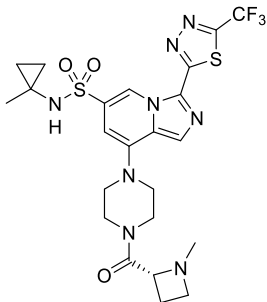
	N-(1-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperidin-4-yl)isobutyramide	(m, 2H), 1.13 (d, J = 6.9 Hz, 6H). LC/MS (ESI) (m/z): 583 [M+H].
Example 269	 (S)-8-(4-(azetidine-2-carbonyl)piperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, MeOD) δ 9.91 (s, 1H), 7.96 (s, 1H), 6.83 (s, 1H), 5.51 – 5.44 (m, 1H), 4.21 – 4.13 (m, 1H), 4.05 – 3.82 (m, 4H), 3.67 – 3.58 (m, 2H), 3.52 – 3.43 (m, 4H), 3.01 – 2.94 (m, 1H), 2.72 – 2.63 (m, 1H), 1.59 – 1.53 (m, 2H), 1.48 – 1.42 (m, 2H). LC/MS (ESI) (m/z): 582 [M+H] ⁺ .
Example 270	 (S)-N-(1-cyanocyclopropyl)-8-(4-(prolyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, MeOD) δ 9.91 (s, 1H), 7.97 (s, 1H), 6.83 (s, 1H), 4.78 – 4.72 (m, 1H), 4.04 – 3.95 (m, 1H), 3.94 – 3.87 (m, 1H), 3.86 – 3.81 (m, 2H), 3.53 – 3.45 (m, 4H), 3.44 – 3.41 (m, 1H), 3.39 – 3.34 (m, 1H), 2.63 – 2.53 (m, 1H), 2.18 – 2.08 (m, 2H), 2.06 – 1.96 (m, 1H), 1.59 – 1.53 (m, 2H), 1.48 – 1.42 (m, 2H). LC/MS (ESI) (m/z): 596 [M+H] ⁺ .
Example 271	 (R)-N-(1-cyanocyclopropyl)-8-(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.62 (s, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 6.73 (s, 1H), 3.85 – 3.73 (m, 4H), 3.57 – 3.42 (m, 2H), 3.40 – 3.35 (m, 2H), 3.30 – 3.22 (m, 2H), 3.17 (s, 1H), 3.14 – 3.07 (m, 2H), 2.21 – 2.10 (m, 1H), 2.00 – 1.90 (m, 1H), 1.40 – 1.31 (m, 2H), 1.30 – 1.23 (m, 2H). LC/MS (ESI) (m/z): 596 [M+H] ⁺ .

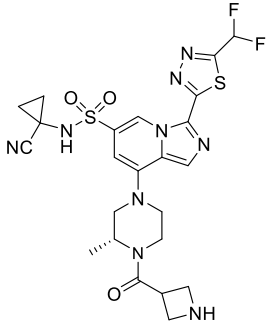
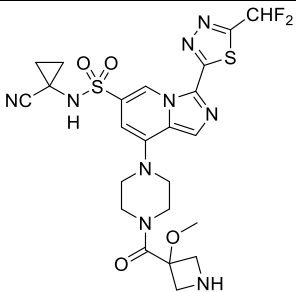
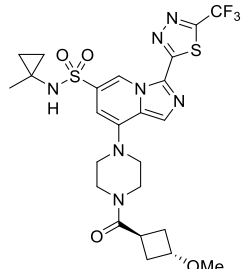
Example 272	 (S)-N-(1-cyanocyclopropyl)-8-(4-(pyrrolidine-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.88 (s, 1H), 8.53 (s, 1H), 7.95 (s, 1H), 6.80 (d, <i>J</i> = 1.0 Hz, 1H), 3.94 – 3.88 (m, 4H), 3.76 – 3.70 (m, 1H), 3.69 – 3.64 (m, 1H), 3.50 – 3.45 (m, 2H), 3.43 – 3.40 (m, 2H), 3.39 – 3.33 (m, 3H), 2.45 – 2.34 (m, 1H), 2.19 – 2.09 (m, 1H), 1.56 – 1.51 (m, 2H), 1.47 – 1.42 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 596 [M+H]⁺.
Example 273	 8-(4-(3-aminocyclobutane-1-carbonyl)piperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.08 (s, 1H), 6.72 (s, 1H), 3.77 – 3.70 (m, 2H), 3.65 – 3.44 (m, 4H), 3.39 – 3.07 (m, 5H), 2.49 – 2.35 (m, 3H), 2.28 – 2.12 (m, 2H), 1.39 – 1.30 (m, 2H), 1.29 – 1.22 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 596 [M+H]⁺.
Example 274	 8-(4-(1-aminocyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.96 (s, 1H), 7.71 (s, 1H), 6.79 (s, 1H), 4.10 – 3.86 (m, 4H), 3.50 – 3.35 (m, 4H), 1.72 – 1.65 (m, 2H), 1.51 – 1.45 (m, 2H), 1.25 – 1.07 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 582 [M+H]⁺.
Example 275		¹H NMR (400 MHz, CDCl₃) δ 9.99 (s, 1H), 7.76 (s, 1H), 6.78 (d, <i>J</i> = 1.0 Hz, 1H), 4.11 – 3.94 (m, 4H), 3.45 – 3.37 (m, 4H), 2.48 (s, 3H), 1.73 – 1.69 (m, 2H), 1.52 – 1.48 (m, 2H), 1.15 – 1.08 (m, 2H), 0.94 – 0.84 (m, 2H).

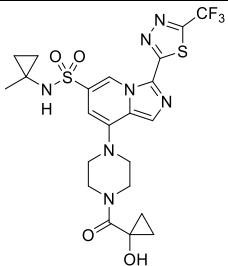
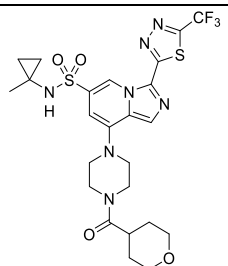
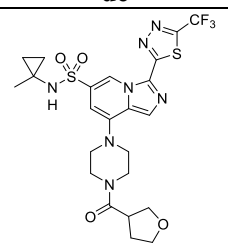
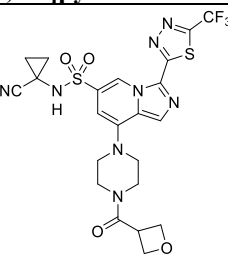
	N-(1-cyanocyclopropyl)-8-(4-(1-(methyl amino)cyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	LC/MS (ESI) (m/z): 596 [M+H] ⁺ .
Example 276	 N-(1-cyanocyclopropyl)-8-(4-(2-hydroxyacetyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 10.06 - 10.00 (m, 1H), 7.80 - 7.73 (m, 1H), 6.78 - 6.74 (m, 1H), 5.74 - 5.68 (m, 1H), 4.31 - 4.24 (m, 2H), 3.98 (s, 2H), 3.59 (s, 2H), 3.45 - 3.39 (m, 4H), 2.04 - 2.01 (m, 1H), 1.76 - 1.72 (m, 2H), 1.56 - 1.54 (m, 2H). LC/MS (ESI) (m/z): 557 [M+H] ⁺ .
Example 277	 8-(4-(azetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 6.72 (s, 1H), 3.97 - 3.91 (m, 2H), 3.88 - 3.82 (m, 2H), 3.77 - 3.74 (m, 2H), 3.33 - 3.29 (m, 7H), 1.16 (s, 3H), 0.78 - 0.69 (m, 2H), 0.49 - 0.42 (m, 2H). LC/MS (ESI) (m/z): 571 [M+H] ⁺ .
Example 278	 N-(1-cyanocyclopropyl)-8-(4-(3-fluoroazetidine-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 10.05 (s, 1H), 7.80 (s, 1H), 6.83 (s, 1H), 4.84 - 4.39 (m, 2H), 4.38 - 4.06 (m, 2H), 4.04 - 3.95 (m, 2H), 3.81 - 3.72 (m, 2H), 3.52 - 3.42 (m, 4H), 1.77 - 1.75 (m, 2H), 1.59 - 1.54 (m, 2H). LC/MS (ESI) (m/z): 600 [M+H] ⁺ .

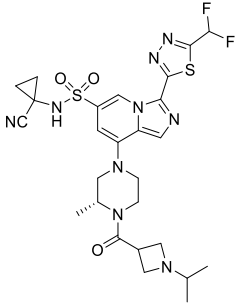
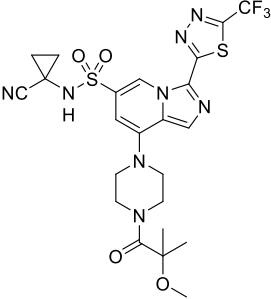
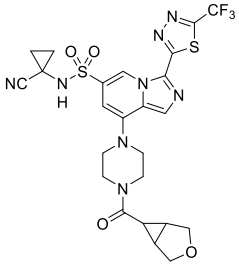
Example 279	 N-(1-cyanocyclopropyl)-8-(4-((2S,4R)-4-hydroxypyrrolidine-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, DMSO-<i>d</i>₆) δ 9.68 (s, 1H), 8.17 (s, 1H), 6.74 (s, 1H), 5.45 (s, 1H), 4.77 - 4.67 (m, 1H), 4.44 (s, 1H), 3.88 - 3.72 (m, 4H), 3.67 - 3.50 (m, 1H), 3.44 - 3.39 (m, 4H), 3.09 - 3.05 (m, 1H), 2.36 - 2.31 (m, 1H), 2.03 - 1.96 (m, 1H), 1.52 - 1.47 (m, 2H), 1.42 - 1.37 (m, 2H). LC/MS (ESI) (m/z): 612 [M+H]⁺.
Example 280	 N-(1-cyanocyclopropyl)-8-(4-(piperazine-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CD₃OD) δ 9.89 (s, 1H), 8.47 (s, 1H), 7.96 (s, 1H), 6.81 (s, 1H), 4.19 - 4.15 (m, 1H), 4.03 - 3.96 (m, 2H), 3.86 - 3.79 (m, 2H), 3.51 - 3.44 (m, 3H), 3.38 - 3.34 (m, 1H), 3.27 - 3.24 (m, 1H), 3.18 - 3.11 (m, 3H), 3.07 - 3.01 (m, 2H), 1.57 - 1.52 (m, 2H), 1.47 - 1.43 (m, 2H). LC/MS (ESI) (m/z): 611 [M+H]⁺.
Example 281	 N-(1-cyanocyclopropyl)-8-(4-(thiazolidine-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO) δ 9.70 - 9.65 (m, 1H), 9.51 (s, 1H), 8.18 (s, 1H), 6.73 (s, 1H), 5.26 (s, 1H), 3.90 - 3.61 (m, 6H), 3.42 - 3.39 (m, 2H), 3.07 - 2.97 (m, 2H), 2.75 - 2.66 (m, 2H), 1.51 - 1.46 (m, 2H), 1.39 (t, <i>J</i> = 6.4 Hz, 2H). LC/MS (ESI) (m/z): 614 [M+H]⁺.

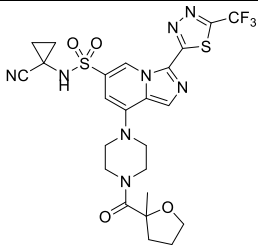
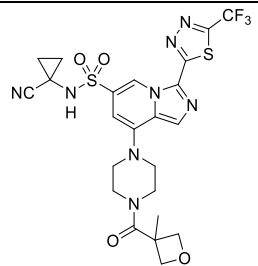
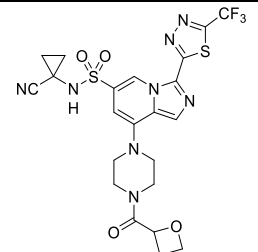
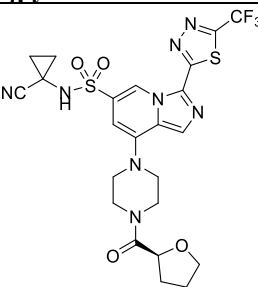
Example 282	 N-(1-methylcyclopropyl)-8-(4-(3,3,3-trifluoro-2-hydroxypropanoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR(400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.15 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.74 (s, 1H), 5.26 - 5.16 (m, 1H), 3.91 - 3.73 (m, 4H), 3.41 - 3.34 (m, 4H), 1.16 (s, 3H), 0.76 - 0.70 (m, 2H), 0.49 - 0.43 (m, 2H). LC/MS (ESI) (m/z): 614 [M+H]$^+$.
Example 283	 N-(1-cyanocyclopropyl)-8-(4-(3-hydroxycyclobutane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, CDCl$_3$) δ 9.99 (s, 1H), 7.75 (s, 1H), 6.73 (s, 1H), 6.05 (s, 1H), 4.33 - 4.18 (m, 1H), 3.91 (s, 2H), 3.69 (s, 2H), 3.36 (d, J = 4.2 Hz, 4H), 2.89 - 2.79 (m, 1H), 2.66 - 2.57 (m, 2H), 2.31 - 2.23 (m, 2H), 1.73 - 1.70 (m, 2H), 1.53 - 1.50 (m, 2H). LC/MS (ESI) (m/z): 597[M+H]$^+$.
Example 284	 (S)-8-(4-(azetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 9.40 (s, 1H), 8.49 (s, 1H), 8.13 (s, 1H), 6.74 (s, 1H), 5.49 - 5.36 (m, 1H), 4.05 - 3.96 (m, 1H), 3.88 - 3.82 (m, 1H), 3.81 - 3.74 (m, 2H), 3.45 - 3.28 (m, 6H), 2.86 - 2.76 (m, 1H), 2.62 - 2.53 (m, 1H), 1.17 (s, 3H), 0.77 - 0.70 (m, 2H), 0.51 - 0.43 (m, 2H). LC/MS (ESI) (m/z): 571 [M+H]$^+$.

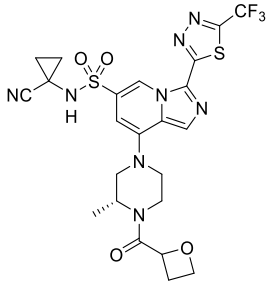
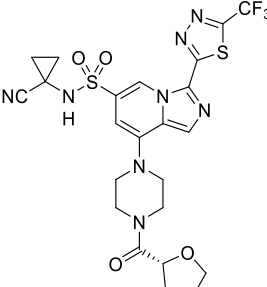
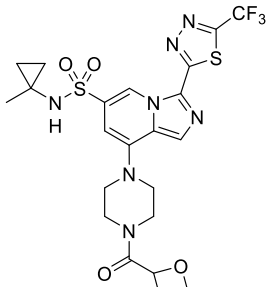
Example 285	 (S)-8-(4-(1-methylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.88 (s, 1H), 9.60 (s, 1H), 8.14 (s, 1H), 6.74 (s, 1H), 5.49 – 5.40 (m, 1H), 4.07 – 3.95 (m, 2H), 3.86 – 3.79 (m, 2H), 3.38 – 3.33 (m, 4H), 2.84 (s, 3H), 2.82 – 2.65 (m, 2H), 2.56 – 2.52 (m, 2H), 1.17 (s, 3H), 0.77 – 0.72 (m, 2H), 0.48 – 0.42 (m, 2H). LC/MS (ESI) (m/z): 585 [M+H]⁺.
Example 286	 (R)-8-(4-(azetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.79 (s, 1H), 7.92 (s, 1H), 6.76 (d, <i>J</i> = 0.9 Hz, 1H), 5.51 – 5.44 (m, 1H), 4.21 – 4.13 (m, 1H), 4.00 – 3.87 (m, 3H), 3.65 – 3.56 (m, 2H), 3.46 – 3.35 (m, 4H), 3.02 – 2.91 (m, 1H), 2.71 – 2.62 (m, 1H), 1.26 (s, 3H), 0.85 – 0.79 (m, 2H), 0.55 – 0.45 (m, 2H). LC/MS (ESI) (m/z): 571 [M+H]⁺.
Example 287	 (R)-8-(4-(1-methylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.80 (s, 1H), 7.93 (s, 1H), 6.76 (d, <i>J</i> = 0.9 Hz, 1H), 5.45 – 5.37 (m, 1H), 4.17 – 4.02 (m, 2H), 3.98 – 3.86 (m, 2H), 3.63 – 3.54 (m, 2H), 3.45 – 3.36 (m, 4H), 2.95 (s, 3H), 2.93 – 2.85 (m, 1H), 2.69 – 2.58 (m, 1H), 1.27 (s, 3H), 0.85 – 0.80 (m, 2H), 0.54 – 0.48 (m, 2H). LC/MS (ESI) (m/z): 585 [M+H]⁺.

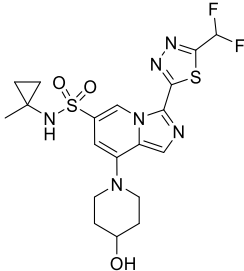
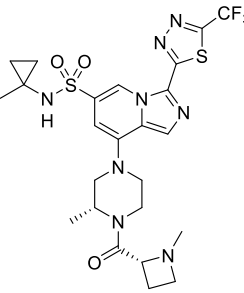
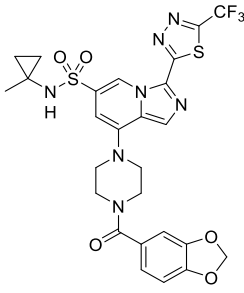
Example 288	 (R)-8-(4-(azetidine-3-carbonyl)-3-methylpiperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.93 (s, 1H), 7.89 (d, <i>J</i> = 4.1 Hz, 1H), 7.34 (t, <i>J</i> = 53.5 Hz, 1H), 6.77 (d, <i>J</i> = 4.2 Hz, 1H), 4.43 – 4.27 (m, 4H), 4.17 – 4.08 (m, 1H), 3.86 – 3.33 (m, 5H), 3.17 – 3.11 (m, 1H), 3.05 – 2.92 (m, 1H), 1.60 – 1.53 (m, 3H), 1.50 – 1.42 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 577 [M+H].
Example 289	 N-(1-cyanocyclopropyl)-3-(5-(difluoroethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(3-methoxyazetidine-3-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CD₃OD) δ 9.91 (s, 1H), 8.49 (s, 1H), 7.92 (s, 1H), 7.34 (t, <i>J</i> = 53.5 Hz, 1H), 6.79 (s, 1H), 4.54 (d, <i>J</i> = 11.9 Hz, 2H), 4.12 (d, <i>J</i> = 12.0 Hz, 2H), 3.98 - 3.88 (m, 2H), 3.79 - 3.70 (m, 2H), 3.48 - 3.41 (m, 4H), 3.34 (s, 3H), 1.57 - 1.50 (m, 2H), 1.48 - 1.42 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 594 [M+H]⁺.
Example 290	 8-(4-((1r,3r)-3-methoxycyclobutane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CDCl₃) δ 9.89 (s, 1H), 7.74 (s, 1H), 6.70 (s, 1H), 5.18 (s, 1H), 4.08 - 4.02 (m, 1H), 3.96 - 3.90 (m, 2H), 3.69 - 3.63 (m, 2H), 3.36 - 3.32 (m, 4H), 3.29 (s, 3H), 2.65 - 2.59 (m, 2H), 2.31 - 2.24 (m, 2H), 1.41 (s, 3H), 0.96 - 0.92 (m, 2H), 0.65 - 0.61 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 600 [M+H]⁺.

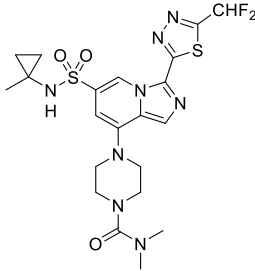
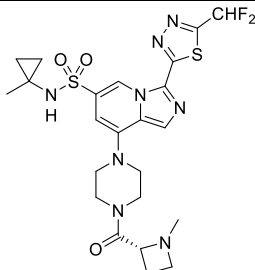
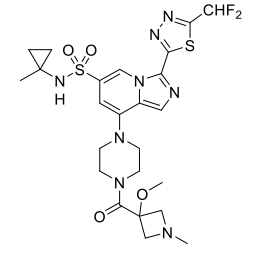
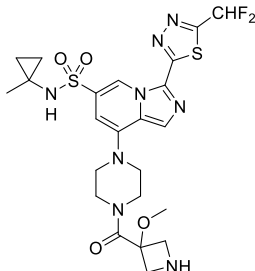
Example 291	 8-(4-(1-hydroxycyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CDCl₃) δ 9.89 (s, 1H), 7.76 (s, 1H), 6.71 (s, 1H), 5.49 (s, 1H), 4.12 - 3.95 (m, 4H), 3.43 - 3.37 (m, 4H), 1.40 (s, 3H), 1.23 - 1.18 (m, 2H), 1.10 - 1.05 (m, 2H), 0.96 - 0.92 (m, 2H), 0.64 - 0.60 (m, 2H). LC/MS (ESI) (m/z): 572 [M+H]⁺.
Example 292	 N-(1-methylcyclopropyl)-8-(4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.90 (s, 1H), 7.75 (s, 1H), 6.71 (s, 1H), 5.15 (s, 1H), 4.08 (d, <i>J</i> = 10.8 Hz, 2H), 3.95 - 3.81 (m, 4H), 3.54 - 3.48 (m, 2H), 3.40 - 3.33 (m, 4H), 2.87 - 2.79 (m, 1H), 2.04 - 1.95 (m, 2H), 1.71 - 1.67 (m, 2H), 1.41 (s, 3H), 0.97 - 0.92 (m, 2H), 0.66 - 0.61 (m, 2H). LC/MS (ESI) (m/z): 600 [M+H]⁺.
Example 293	 N-(1-methylcyclopropyl)-8-(4-(tetrahydrofuran-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.87 (s, 1H), 7.72 (s, 1H), 6.70 (s, 1H), 5.24 (s, 1H), 4.08 - 4.03 (m, 1H), 3.97 - 3.89 (m, 5H), 3.81 (s, 2H), 3.39 - 3.29 (m, 5H), 2.33 - 2.25 (m, 1H), 2.18 - 2.10 (m, 1H), 1.39 (s, 3H), 0.94 - 0.90 (m, 2H), 0.63 - 0.58 (m, 2H). LC/MS (ESI) (m/z): 586 [M+H]⁺.
Example 294	 N-(1-cyanocyclopropyl)-8-(4-(oxetane-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), 8.45 (s, 1H), 8.10 (s, 1H), 6.71 (d, <i>J</i> = 0.9 Hz, 1H), 4.77 - 4.68 (m, 4H), 4.20 (dd, <i>J</i> = 15.5, 8.4 Hz, 1H), 3.81 - 3.70 (m, 2H), 3.48 - 3.41 (m, 2H), 3.31 - 3.25 (m, 4H), 1.15 (s, 3H),

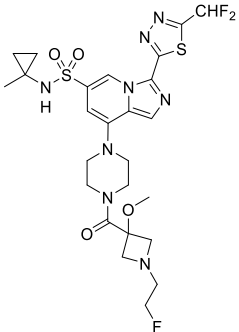
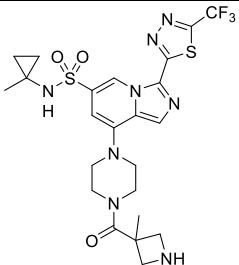
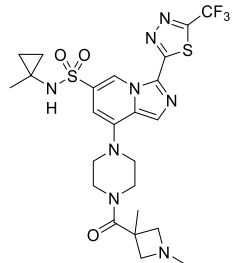
	carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	0.75 – 0.68 (m, 2H), 0.48 – 0.41 (m, 2H). LC/MS (ESI) (m/z): 572 [M+H] ⁺ .
Example 295	 (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-isopropylazetidine-3-carbonyl)-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, MeOD) δ 9.92 (s, 1H), 8.48 (s, 1H), 7.89 (d, J = 3.6 Hz, 1H), 7.34 (t, J = 53.6 Hz, 1H), 6.77 (d, J = 4.1 Hz, 1H), 4.18 – 3.40 (m, 10H), 3.16 – 3.11 (m, 1H), 3.05 – 2.90 (m, 2H), 1.61 – 1.53 (m, 3H), 1.50 – 1.41 (m, 4H), 1.17 – 1.12 (m, 6H). LC/MS (ESI) (m/z): 620 [M+H] ⁺ .
Example 296	 N-(1-cyanocyclopropyl)-8-(4-(2-methoxy-2-methylpropanoyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 10.02 (s, 1H), 7.79 (s, 1H), 6.74 (s, 1H), 5.71 (s, 1H), 4.36 – 4.25 (m, 2H), 4.01 – 3.91 (m, 2H), 3.43 – 3.39 (m, 4H), 3.31 (s, 3H), 1.76 – 1.72 (m, 2H), 1.55 – 1.51 (m, 8H). LC/MS (ESI) (m/z): 599 [M+H] ⁺ .
Example 297	 8-(4-(3-oxabicyclo[3.1.0]hexane-6-carbonyl)piperazin-1-yl)-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CDCl ₃) δ 10.01 (s, 1H), 7.79 (s, 1H), 6.74 (s, 1H), 6.02 (s, 1H), 3.99 – 3.96 (m, 2H), 3.95 – 3.90 (m, 4H), 3.84 – 3.80 (m, 2H), 3.48 – 3.36 (m, 4H), 2.26 (s, 2H), 1.82 – 1.79 (m, 1H), 1.76 – 1.72 (m, 2H), 1.56 – 1.53 (m, 2H). LC/MS (ESI) (m/z): 609 [M+H] ⁺ .

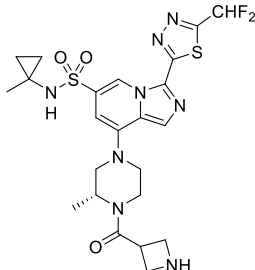
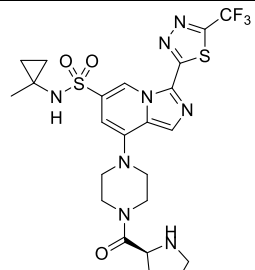
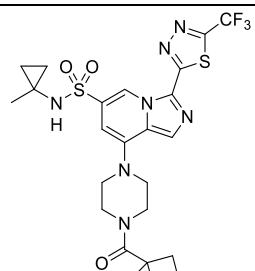
Example 298	 N-(1-cyanocyclopropyl)-8-(4-(2-methyltetrahydrofuran-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.98 (s, 1H), 7.76 (s, 1H), 6.71 (s, 1H), 5.93 (s, 1H), 4.07 – 3.94 (m, 3H), 3.89 – 3.71 (m, 2H), 3.47 – 3.26 (m, 4H), 2.88 – 2.81 (m, 1H), 1.96 – 1.86 (m, 2H), 1.76 – 1.62 (m, 4H), 1.59 (s, 3H), 1.54 – 1.52 (m, 2H). LC/MS (ESI) (m/z): 611[M+H]⁺.
Example 299	 N-(1-cyanocyclopropyl)-8-(4-(3-methyltetrahydrofuran-3-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (s, 1H), 9.50 (s, 1H), 8.13 (s, 1H), 6.73 (s, 1H), 4.91 – 4.85 (m, 2H), 4.36 – 4.30 (m, 2H), 3.81 – 3.72 (m, 2H), 3.40 – 3.35 (m, 4H), 3.31 – 3.24 (m, 2H), 1.63 – 1.60 (m, 3H), 1.52 – 1.47 (m, 2H), 1.42 – 1.36 (m, 2H). LC/MS (ESI) (m/z): 597 [M+H]⁺.
Example 300	 N-(1-cyanocyclopropyl)-8-(4-(oxetane-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.48 (s, 1H), 8.15 (s, 1H), 6.71 (s, 1H), 5.51 – 5.45 (m, 1H), 4.61 – 4.55 (m, 1H), 4.47 – 4.41 (m, 1H), 3.82 – 3.72 (m, 2H), 3.65 – 3.54 (m, 2H), 3.44 – 3.34 (m, 4H), 2.97 – 2.86 (m, 1H), 2.82 – 2.72 (m, 1H), 1.53 – 1.46 (m, 2H), 1.41 – 1.34 (m, 2H). LC/MS (ESI) (m/z): 583 [M+H]⁺.
Example 301	 (S)-N-(1-cyanocyclopropyl)-8-(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.66 (s, 1H), 9.50 (s, 1H), 8.14 (s, 1H), 6.72 (s, 1H), 4.80 – 4.69 (m, 1H), 3.90 – 3.69 (m, 6H), 3.42 – 3.36 (m, 2H), 3.32 – 3.24 (m, 2H), 2.17 – 1.98 (m, 2H), 1.93 – 1.80 (m, 2H), 1.52 – 1.44 (m, 2H), 1.44 – 1.36 (m, 2H). LC/MS (ESI) (m/z): 597

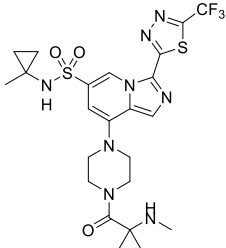
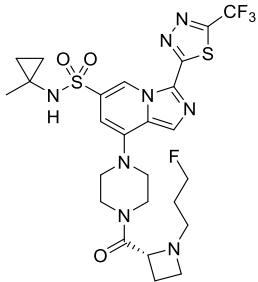
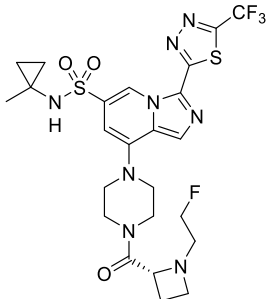
	ydrofuran-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	[M+H] ⁺ .
Example 302	 N-(1-cyanocyclopropyl)-8-((3R)-3-methyl-4-(oxetane-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.65 (s, 1H), 9.50 (s, 1H), 8.03 (s, 1H), 6.77 – 6.66 (m, 1H), 5.54 – 5.42 (m, 1H), 4.86 – 4.44 (m, 2H), 4.43 – 3.97 (m, 2H), 3.81 – 3.59 (m, 3H), 3.14 – 3.04 (m, 1H), 2.96 – 2.70 (m, 3H), 1.52 – 1.47 (m, 2H), 1.44 – 1.30 (m, 5H). LC/MS (ESI) (m/z): 597 [M+H]⁺.
Example 303	 (R)-N-(1-cyanocyclopropyl)-8-(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 10.01 (s, 1H), 7.77 (s, 1H), 6.79 (s, 1H), 6.24 (s, 1H), 4.73 - 4.66 (m, 1H), 4.08 - 3.80 (m, 6H), 3.48 - 3.29 (m, 4H), 2.44 - 2.34 (m, 1H), 2.15 - 1.96 (m, 3H), 1.75 - 1.71 (m, 2H), 1.54 - 1.51 (m, 2H). LC/MS (ESI) (m/z): 597 [M+H]⁺.
Example 304	 N-(1-methylcyclopropyl)-8-(4-(oxetane-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), 8.45 (s, 1H), 8.12 (s, 1H), 6.73 (s, 1H), 5.48 (t, <i>J</i> = 7.6 Hz, 1H), 4.62 – 4.55 (m, 1H), 4.47 – 4.41 (m, 1H), 3.82 – 3.73 (m, 2H), 3.64 – 3.54 (m, 2H), 3.28 – 3.13 (m, 4H), 2.95 – 2.80 (m, 2H), 1.16 (s, 3H), 0.76 – 0.71 (m, 2H), 0.49 – 0.44 (m, 2H). LC/MS (ESI) (m/z): 572 [M+H]⁺.

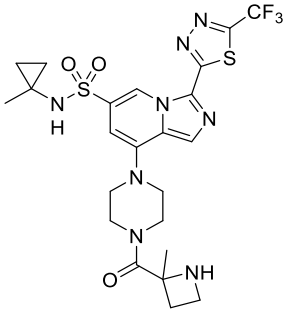
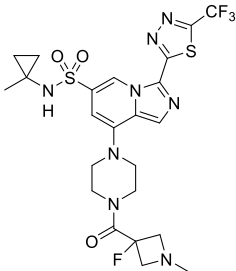
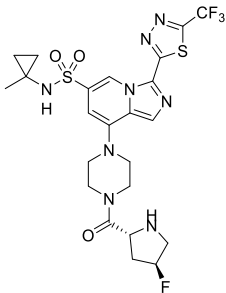
Example 305	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxypiperidin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.56 (s, 1H), 8.42 (s, 1H), 7.96 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.67 (s, 1H), 4.82 (d, <i>J</i> = 4.0 Hz, 1H), 3.82 – 3.74 (m, 1H), 3.64 – 3.56 (m, 2H), 3.13 – 3.05 (m, 2H), 2.00 – 1.92 (m, 2H), 1.70 – 1.61 (m, 2H), 1.15 (s, 3H), 0.76 – 0.71 (m, 2H), 0.48 – 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 485 [M+H]⁺.
Example 306	 8-((R)-3-methyl-4-((R)-1-methylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), 8.48 (s, 1H), 8.00 (s, 1H), 6.72 (s, 1H), 4.76 – 4.32 (m, 1H), 3.87 – 3.77 (m, 1H), 3.71 – 3.60 (m, 2H), 3.54 – 3.46 (m, 2H), 3.20 – 3.09 (m, 2H), 3.07 – 3.03 (m, 2H), 2.91 – 2.86 (m, 1H), 2.77 – 2.67 (m, 4H), 1.41 (s, 3H), 1.17 (s, 3H), 0.76 – 0.68 (m, 2H), 0.51 – 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 599[M+H]⁺
Example 307	 8-(4-(benzo[d][1,3]dioxole-5-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), 8.45 (s, 1H), 8.10 (s, 1H), 7.07 (s, 1H), 7.00 (s, 2H), 6.74 (s, 1H), 6.13 – 6.08 (m, 2H), 3.97 – 3.64 (m, 4H), 3.45 – 3.36 (m, 4H), 1.16 (s, 3H), 0.78 – 0.70 (m, 2H), 0.50 – 0.42 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 636 [M+H]⁺.

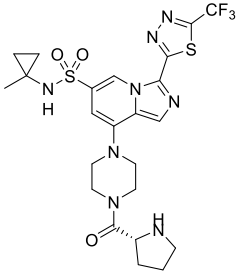
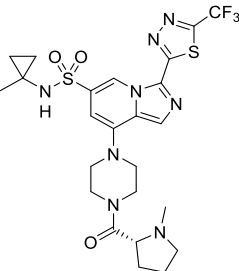
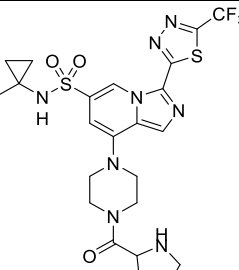
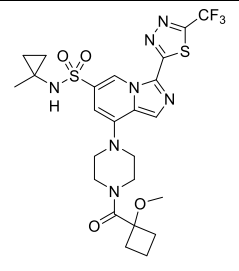
Example 308	 4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,N-dimethylpiperazine-1-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.42 (s, 1H), 8.05 (s, 1H), 7.68 (t, <i>J</i> = 53.3 Hz, 1H), 6.71 (s, 1H), 3.60 – 3.37 (m, 8H), 2.89 – 2.77 (m, 6H), 1.16 (s, 3H), 0.81 – 0.69 (m, 2H), 0.55 – 0.40 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 541 [M+H]⁺.
Example 309	 (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-methylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.62 (s, 1H), 8.46 (s, 1H), 8.09 (s, 1H), 7.69 (t, <i>J</i> = 53.6 Hz, 1H), 6.70 (s, 1H), 5.47 – 5.37 (m, 1H), 4.01 – 3.92 (m, 2H), 3.85 – 3.75 (m, 2H), 3.51 – 3.47 (m, 2H), 3.35 – 3.28 (m, 5H), 2.83 (s, 3H), 2.80 – 2.73 (m, 1H), 1.17 (s, 3H), 0.78 – 0.68 (m, 2H), 0.49 – 0.42 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 567 [M+H]⁺.
Example 310	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(3-methoxy-1-methylazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CD₃OD) δ 9.83 (s, 1H), 7.91 (s, 1H), 7.33 (t, <i>J</i> = 53.5 Hz, 1H), 6.74 (s, 1H), 4.22 - 4.16 (m, 2H), 3.95 - 3.90 (m, 2H), 3.86 - 3.81 (m, 2H), 3.78 - 3.74 (m, 2H), 3.41 - 3.37 (m, 4H), 3.32 (s, 3H), 2.67 (s, 3H), 1.26 (s, 3H), 0.85 - 0.81 (m, 2H), 0.53 - 0.48 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 597 [M+H]⁺.
Example 311		¹H NMR(400 MHz, CD₃OD) δ 9.83 (s, 1H), 7.91 (s, 1H), 7.34 (t, <i>J</i> = 53.5 Hz, 1H), 6.74 (s, 1H), 4.57 (d, <i>J</i> = 11.5 Hz, 2H), 4.14 (d, <i>J</i> = 11.4 Hz, 2H), 3.97 - 3.91 (m, 2H), 3.79 - 3.73 (m, 2H), 3.43 - 3.38 (m, 4H), 3.35 (s, 3H),

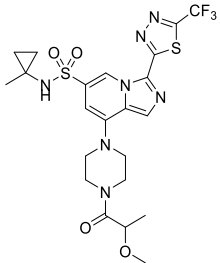
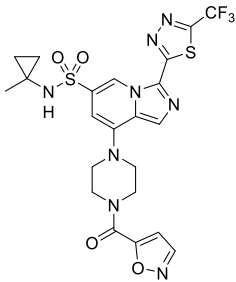
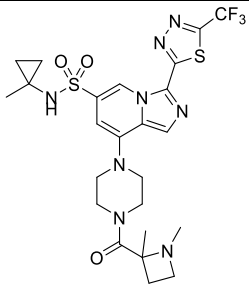
	3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(3-methoxyazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	1.27 (s, 3H), 0.86 - 0.80 (m, 2H), 0.54 - 0.48 (m, 2H). LC/MS (ESI) (m/z): 583 [M+H] ⁺ .
Example 312	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(1-(2-fluoroethyl)-3-methoxyazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR(400 MHz, CD ₃ OD) δ 9.82 (s, 1H), 7.91 (s, 1H), 7.33 (t, <i>J</i> = 53.6 Hz, 1H), 6.73 (d, <i>J</i> = 0.9 Hz, 1H), 4.58 - 4.54 (m, 1H), 4.46 - 4.42 (m, 1H), 3.95 - 3.90 (m, 4H), 3.79 - 3.75 (m, 2H), 3.60 - 3.56 (m, 2H), 3.40 - 3.36 (m, 4H), 3.28 (s, 3H), 2.97 - 2.93 (m, 1H), 2.90 - 2.86 (m, 1H), 1.25 (s, 3H), 0.84 - 0.80 (m, 2H), 0.52 - 0.48 (m, 2H). LC/MS (ESI) (m/z): 629 [M+H] ⁺ .
Example 313	 8-(4-(3-methylazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.83 (s, 1H), 7.95 (s, 1H), 6.79 (s, 1H), 4.65 - 4.34 (m, 2H), 4.04 - 3.82 (m, 4H), 3.55 - 3.38 (m, 6H), 1.73 (s, 3H), 1.29 (s, 3H), 0.87 - 0.77 (m, 2H), 0.57 - 0.48 (m, 2H). LC/MS (ESI) (m/z): 585 [M+H] ⁺ .
Example 314	 8-(4-(1,3-dimethylazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.82 (s, 1H), 7.95 (s, 1H), 6.78 (s, 1H), 3.95 - 3.85 (m, 4H), 3.75 - 3.70 (m, 2H), 3.57 - 3.49 (m, 2H), 3.43 - 3.37 (m, 4H), 2.60 (s, 3H), 1.68 (s, 3H), 1.28 (s, 3H), 0.87 - 0.81 (m, 2H), 0.55 - 0.50 (m, 2H). LC/MS (ESI) (m/z): 599 [M+H] ⁺ .

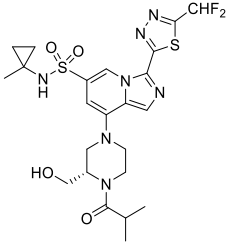
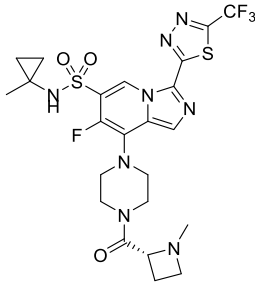
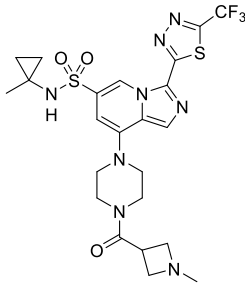
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Example 315	 (R)-8-(4-(azetidine-3-carbonyl)-3-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.67 (d, <i>J</i> = 6.2 Hz, 1H), 4.74 – 4.34 (m, 1H), 3.97 – 3.83 (m, 4H), 3.70 – 3.61 (m, 2H), 3.28 – 2.78 (m, 6H), 1.44 – 1.31 (m, 3H), 1.16 (s, 3H), 0.78 – 0.67 (m, 2H), 0.50 – 0.40 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 567 [M+H] ⁺ .
Example 316	 (S)-N-(1-methylcyclopropyl)-8-(4-propylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.83 (s, 1H), 7.97 (s, 1H), 6.79 (s, 1H), 4.52 – 4.47 (m, 1H), 4.01 – 3.81 (m, 4H), 3.46 – 3.38 (m, 4H), 3.24 – 3.13 (m, 2H), 2.66 – 2.27 (m, 1H), 2.08 – 1.90 (m, 3H), 1.29 (s, 3H), 0.88 – 0.81 (m, 2H), 0.56 – 0.49 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 585 [M+H] ⁺ .
Example 317	 8-(4-(3-fluoroazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, MeOD) δ 9.82 (s, 1H), 7.95 (s, 1H), 6.77 (d, <i>J</i> = 1.0 Hz, 1H), 4.82 – 4.77 (m, 2H), 4.58 – 4.45 (m, 2H), 4.02 – 3.89 (m, 2H), 3.81 – 3.68 (m, 2H), 3.45 – 3.37 (m, 4H), 1.27 (s, 3H), 0.88 – 0.76 (m, 2H), 0.60 – 0.42 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 589 [M+H] ⁺ .

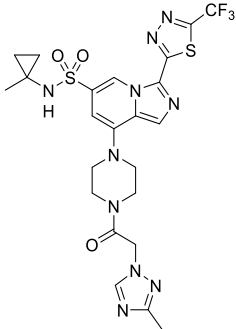
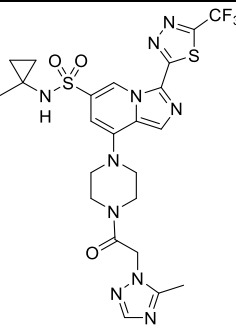
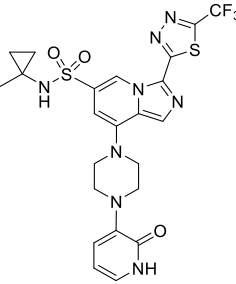
Example 318	 8-(4-(1-(methylamino)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.82 (s, 1H), 7.97 (s, 1H), 6.78 (s, 1H), 4.09 – 3.90 (m, 4H), 3.45 – 3.36 (m, 4H), 2.42 (s, 3H), 1.28 (s, 3H), 1.07 – 0.99 (m, 2H), 0.90 – 0.82 (m, 4H), 0.57 – 0.50 (m, 2H). LC/MS (ESI) (m/z): 585 [M+H]⁺.
Example 319	 (R)-8-(4-(1-(3-fluoropropyl)azetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 6.74 (s, 1H), 5.68 – 5.29 (m, 1H), 4.60 (t, <i>J</i> = 5.7 Hz, 1H), 4.49 (t, <i>J</i> = 5.6 Hz, 1H), 4.05 – 3.89 (m, 2H), 3.83 – 3.78 (m, 2H), 3.65 – 3.59 (m, 1H), 3.53 – 3.49 (m, 2H), 3.39 – 3.36 (m, 3H), 3.27 – 3.23 (m, 1H), 3.19 – 3.02 (m, 2H), 2.82 – 2.71 (m, 1H), 2.00 – 1.85 (m, 2H), 1.17 (s, 3H), 0.75 – 0.71 (m, 2H), 0.49 – 0.45 (m, 2H). LC/MS (ESI) (m/z): 631 [M+H]⁺.
Example 320	 (R)-8-(4-(1-(2-fluoroethyl)azetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.82 (s, 1H), 7.94 (s, 1H), 6.77 (s, 1H), 5.58 – 5.43 (m, 1H), 4.80 – 4.77 (m, 1H), 4.69 – 4.65 (m, 1H), 4.17 – 4.07 (m, 2H), 4.00 – 3.94 (m, 1H), 3.91 – 3.85 (m, 1H), 3.68 – 3.53 (m, 4H), 3.44 – 3.36 (m, 4H), 2.91 – 2.83 (m, 1H), 2.73 – 2.63 (m, 1H), 1.27 (s, 3H), 0.85 – 0.81 (m, 2H), 0.53 – 0.49 (m, 2H). LC/MS (ESI) (m/z): 617 [M+H]⁺.

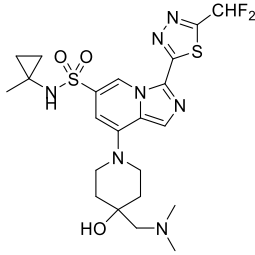
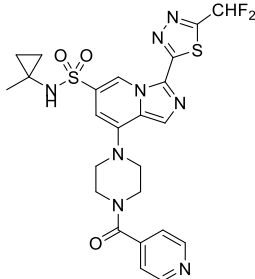
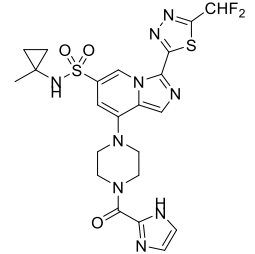
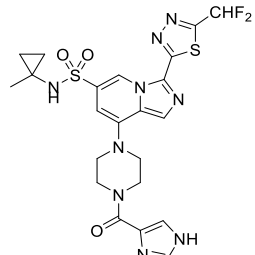
Example 321	 8-(4-(2-methylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.46 (s, 1H), 8.11 (s, 1H), 6.74 (s, 1H), 3.82 – 3.73 (m, 2H), 3.64 – 3.57 (m, 2H), 3.49 – 3.45 (m, 2H), 3.30 – 3.25 (m, 2H), 3.22 – 3.12 (m, 2H), 2.68 – 2.61 (m, 1H), 2.31 – 2.21 (m, 1H), 1.50 (s, 3H), 1.24 (d, <i>J</i> = 5.8 Hz, 1H), 1.20 – 1.11 (m, 3H), 0.76 – 0.69 (m, 2H), 0.51 – 0.42 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 585 [M+H]⁺.
Example 322	 8-(4-(3-fluoro-1-methylazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.82 (s, 1H), 7.95 (s, 1H), 6.77 (s, 1H), 4.81 – 4.77 (m, 2H), 4.70 – 4.60 (m, 2H), 3.97 – 3.89 (m, 2H), 3.78 – 3.72 (m, 2H), 3.44 – 3.39 (m, 4H), 3.05 (s, 3H), 1.27 (s, 3H), 0.86 – 0.79 (m, 2H), 0.54 – 0.49 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 603 [M+H]⁺.
Example 323	 8-(4-((2R,4S)-4-fluoropyrrolidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.82 (s, 1H), 7.95 (s, 1H), 6.78 (s, 1H), 5.53 (d, <i>J</i> = 51.5 Hz, 1H), 5.06 – 4.99 (m, 1H), 4.00 – 3.86 (m, 2H), 3.85 – 3.77 (m, 2H), 3.76 – 3.53 (m, 2H), 3.47 – 3.38 (m, 4H), 3.04 – 2.90 (m, 1H), 2.41 – 2.21 (m, 1H), 1.27 (s, 3H), 0.86 – 0.80 (m, 2H), 0.55 – 0.49 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 603 [M+H]⁺.

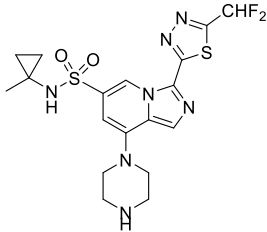
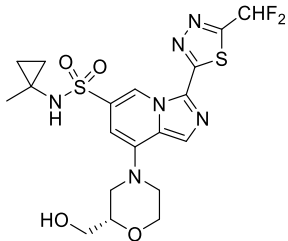
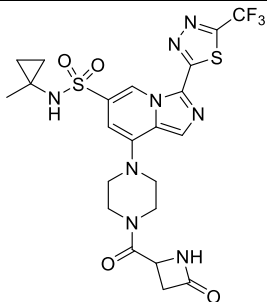
Example 324	 (R)-N-(1-methylcyclopropyl)-8-(4-prolyl piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CD₃OD) δ 9.82 - 9.79 (m, 1H), 7.95 (s, 1H), 6.77 (s, 1H), 4.55 - 4.49 (m, 1H), 4.00 - 3.93 (m, 1H), 3.92 - 3.87 (m, 1H), 3.87 - 3.80 (m, 2H), 3.45 - 3.41 (m, 2H), 3.40 - 3.33 (m, 3H), 3.22 - 3.16 (m, 1H), 2.51 - 2.41 (m, 1H), 2.06 - 1.92 (m, 3H), 1.27 (s, 3H), 0.85 - 0.81 (m, 2H), 0.53 - 0.49 (m, 2H). LC/MS (ESI) (m/z): 585 [M+H]⁺.
Example 325	 8-(4-(methyl-D-prolyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CD₃OD) δ 9.81 - 9.78 (m, 1H), 7.94 (s, 1H), 6.76 (s, 1H), 3.98 - 3.90 (m, 2H), 3.88 - 3.80 (m, 3H), 3.47 - 3.36 (m, 5H), 2.78 - 2.69 (m, 1H), 2.64 - 2.60 (m, 3H), 2.52 - 2.42 (m, 1H), 2.09 - 2.01 (m, 1H), 2.00 - 1.90 (m, 2H), 1.26 (s, 3H), 0.85 - 0.80 (m, 2H), 0.53 - 0.48 (m, 2H). LC/MS (ESI) (m/z): 599 [M+H]⁺.
Example 326	 N-(1-methylcyclopropyl)-8-(4-(thiazolidine-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.84 (s, 1H), 7.99 (s, 1H), 6.80 (s, 1H), 5.32 (s, 1H), 4.07 - 3.96 (m, 1H), 3.91 - 3.76 (m, 4H), 3.52 - 3.37 (m, 4H), 3.15 (t, <i>J</i> = 6.5 Hz, 2H), 3.08 - 3.00 (m, 1H), 2.98 - 2.90 (m, 1H), 1.28 (s, 3H), 0.87 - 0.80 (m, 2H), 0.58 - 0.48 (m, 2H). LC/MS (ESI) (m/z): 603 [M+H]⁺.
Example 327	 8-(4-(1-methoxycyclobutane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.82 (s, 1H), 7.97 (s, 1H), 6.78 (d, <i>J</i> = 1.0 Hz, 1H), 3.96 - 3.90 (m, 4H), 3.44 - 3.37 (m, 4H), 3.20 (s, 3H), 2.70 - 2.60 (m, 2H), 2.30 - 2.19 (m, 2H), 1.96 - 1.82 (m, 1H), 1.75 - 1.58 (m, 1H), 1.27 (s, 3H), 0.87 - 0.81 (m, 2H), 0.57 - 0.49 (m, 2H).

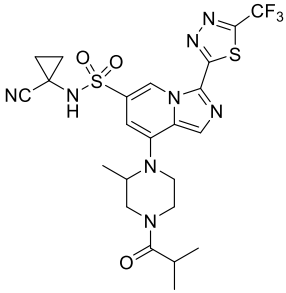
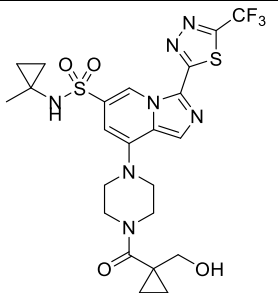
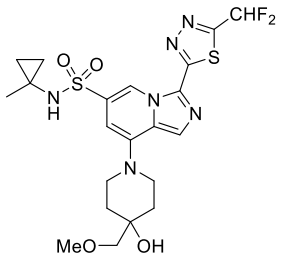
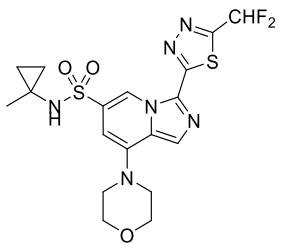
	)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	2H). LC/MS (ESI) (m/z): 600 [M+H]⁺.
Example 328	 8-(4-(2-methoxypropanoyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), , 8.45 (s, 1H), 8.12 (s, 1H), 6.73 (s, 1H), 4.33 – 4.26 (m, 1H), 3.87 – 3.75 (m, 4H), 3.39 – 3.30 (m, 4H), 3.25 (s, 3H), 1.30 – 1.26 (m, 3H), 1.16 (s, 3H), 0.76 – 0.69 (m, 2H), 0.48 – 0.43 (m, 2H). LC/MS (ESI) (m/z): 574 [M+H]⁺.
Example 329	 8-(4-(isoxazole-5-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.80 (d, <i>J</i> = 1.9 Hz, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 7.02 (d, <i>J</i> = 1.8 Hz, 1H), 6.74 (s, 1H), 3.99 – 3.82 (m, 4H), 3.52 – 3.40 (m, 4H), 1.16 (s, 3H), 0.77 – 0.71 (m, 2H), 0.48 – 0.41 (m, 2H). LC/MS (ESI) (m/z): 583 [M+H]⁺.
Example 330	 8-(4-(1,2-dimethylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.47 (s, 1H), 8.11 (s, 1H), 6.74 (s, 1H), 3.95 – 3.65 (m, 6H), 3.61 – 3.54 (m, 4H), 2.88 – 2.79 (m, 2H), 2.68 (s, 3H), 1.75 (s, 3H), 1.17 (s, 3H), 0.78 – 0.68 (m, 2H), 0.52 – 0.41 (m, 2H). LC/MS (ESI) (m/z): 599 [M+H]⁺.

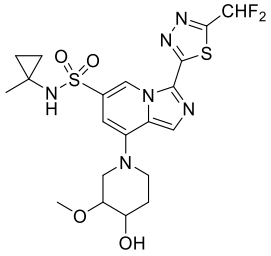
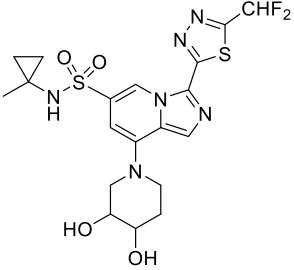
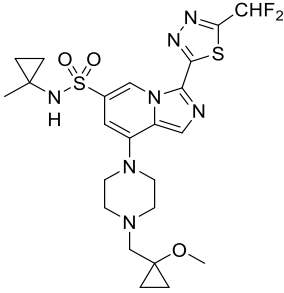
Example 331	 (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(hydroxymethyl)-4-isobutrylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR(400 MHz, CD₃OD) δ 9.83 (s, 1H), 8.15 (d, <i>J</i> = 41.5 Hz, 1H), 7.26 (t, <i>J</i> = 53.5 Hz, 1H), 6.74 (s, 1H), 4.78 - 4.72 (m, 1H), 4.60 (d, <i>J</i> = 14.0 Hz, 1H), 4.29 - 4.21 (m, 1H), 4.15 - 4.06 (m, 2H), 3.69 - 3.65 (m, 1H), 3.15 - 2.96 (m, 3H), 2.93 - 2.85 (m, 1H), 1.26 (s, 3H), 1.18 - 1.13 (m, 6H), 0.85 - 0.81 (m, 2H), 0.53 - 0.49 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 570 [M+H]⁺.
Example 332	 (R)-7-fluoro-8-(4-(1-methylazetidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.64 (d, <i>J</i> = 5.2 Hz, 1H), 8.81 (s, 1H), 8.03 (s, 1H), 5.47 - 5.38 (m, 1H), 4.00 - 3.93 (m, 2H), 3.79 - 3.73 (m, 2H), 3.45 - 3.42 (m, 6H), 2.85 - 2.82 (m, 3H), 2.80 - 2.77 (m, 1H), 2.69 - 2.66 (m, 1H), 1.27 (s, 3H), 0.82 - 0.77 (m, 2H), 0.54 - 0.49 (m, 2H). LC/MS (ESI) <i>m/z</i>: 603 [M+H]⁺.
Example 333	 8-(4-(1-methylazetidine-3-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.48 (s, 1H), 8.12 (s, 1H), 6.72 (s, 1H), 4.49 - 4.34 (m, 2H), 4.18 - 4.07 (m, 2H), 4.03 - 3.82 (m, 1H), 3.81 - 3.72 (m, 2H), 3.61 - 3.54 (m, 2H), 3.34 - 3.28 (m, 4H), 2.91 - 2.78 (m, 3H), 1.17 (s, 3H), 0.78 - 0.67 (m, 2H), 0.51 - 0.38 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 585 [M+H]⁺

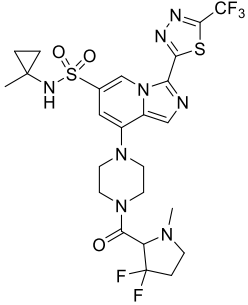
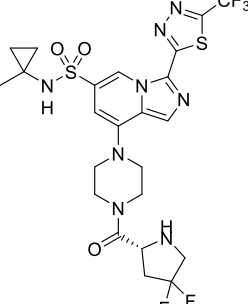
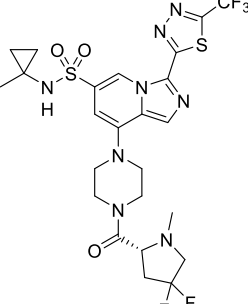
Example 334	 8-(4-(2-(3-methyl-1H-1,2,4-triazol-1-yl)acetyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.60 (s, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 8.15 (s, 1H), 6.74 (s, 1H), 5.27 (s, 2H), 3.81 - 3.73 (m, 4H), 3.44 - 3.36 (m, 4H), 2.25 (s, 3H), 1.17 (s, 3H), 0.75 - 0.71 (m, 2H), 0.49 - 0.44 (m, 2H). LC/MS (ESI) (m/z): 611 M +H)⁺.
Example 335	 8-(4-(2-(5-methyl-1H-1,2,4-triazol-1-yl)acetyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.59 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 7.79 (s, 1H), 6.73 (s, 1H), 5.31 (s, 2H), 3.82 - 3.73 (m, 4H), 3.45 - 3.36 (m, 4H), 2.33 (s, 3H), 1.16 (s, 3H), 0.75 - 0.71 (m, 2H), 0.48 - 0.44 (m, 2H). LC/MS (ESI) (m/z): 611 M +H)⁺.
Example 336	 N-(1-methylcyclopropyl)-8-(4-(2-oxo-1,2-dihydropyridin-3-yl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.80 (s, 1H), 7.93 (s, 1H), 7.11 (dd, <i>J</i> = 6.5, 1.6 Hz, 1H), 7.07 (dd, <i>J</i> = 7.3, 1.5 Hz, 1H), 6.79 (s, 1H), 6.39 (t, <i>J</i> = 6.9 Hz, 1H), 3.54 - 3.50 (m, 4H), 3.39 - 3.35 (m, 4H), 1.27 (s, 3H), 0.86 - 0.82 (m, 2H), 0.53 - 0.49 (m, 2H). LC/MS (ESI) (m/z): 581 [M+H]⁺.

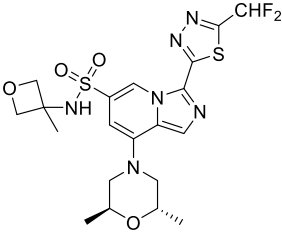
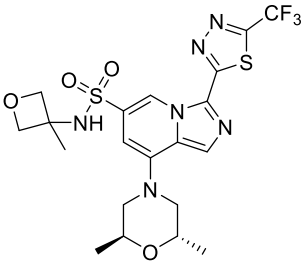
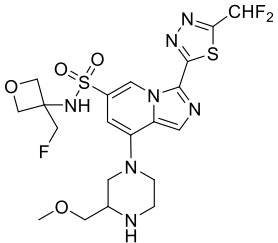
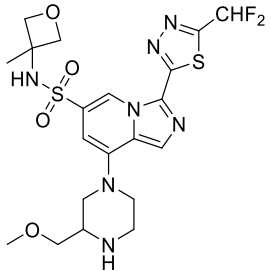
Example 337	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-((dimethylamino)methyl)-4-hydroxypiperidin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.56 (s, 1H), 8.44 (s, 1H), 7.96 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.70 (s, 1H), 3.51 - 3.48 (m, 2H), 3.28 - 3.22 (m, 2H), 2.48 (s, 2H), 2.40 (s, 6H), 1.86 - 1.79 (m, 2H), 1.71 (d, <i>J</i> = 13.2 Hz, 2H), 1.16 (s, 3H), 0.75 - 0.71 (m, 2H), 0.47 - 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 542 (<i>M</i> + <i>H</i>)⁺.
Example 338	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isonicotinoylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.61 (s, 1H), 8.71 (d, <i>J</i> = 5.8 Hz, 2H), 8.44 (s, 1H), 8.06 (s, 1H), 7.75 (t, <i>J</i> = 53.3 Hz, 1H), 7.49 (d, <i>J</i> = 5.9 Hz, 2H), 6.71 (s, 1H), 3.98 - 3.88 (m, 2H), 3.60 - 3.51 (m, 2H), 3.47 - 3.40 (m, 2H), 3.38 - 3.34 (m, 2H), 1.16 (s, 3H), 0.76 - 0.71 (m, 2H), 0.48 - 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 575 [<i>M</i>+<i>H</i>]⁺.
Example 339	 8-(4-(1H-imidazole-2-carbonyl)piperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.61 (s, 1H), 8.42 (s, 1H), 8.11 (s, 1H), 7.69 (t, <i>J</i> = 53.1 Hz, 1H), 7.29 (s, 1H), 7.11 (s, 1H), 6.73 (s, 1H), 4.84 - 4.72 (m, 2H), 3.98 - 3.87 (m, 2H), 3.49 - 3.41 (m, 4H), 1.16 (s, 3H), 0.76 - 0.71 (m, 2H), 0.49 - 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 564 [<i>M</i>+<i>H</i>]⁺.
Example 340	 8-(4-(1H-imidazole-4-carbonyl)piperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.83 (s, 1H), 7.94 (s, 1H), 7.78 (s, 1H), 7.64 (s, 1H), 7.26 (t, <i>J</i> = 53.5 Hz, 1H), 6.75 (s, 1H), 4.28 - 4.04 (m, 4H), 3.46 - 3.42 (m, 4H), 1.25 (s, 3H), 0.84 - 0.81 (m, 2H), 0.52 - 0.48 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 564 [<i>M</i>+<i>H</i>]⁺.

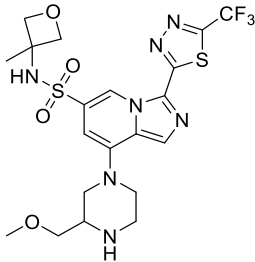
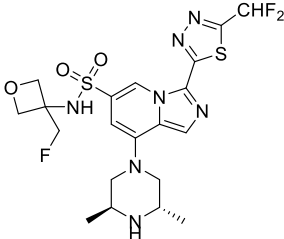
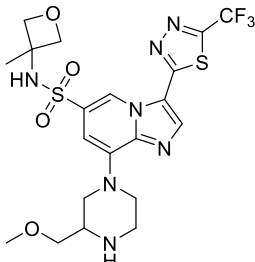
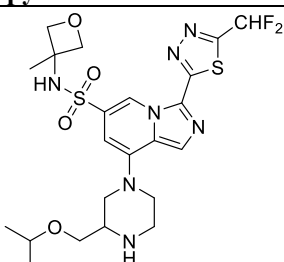
	n-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 341	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.60 (s, 1H), 8.02 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.70 (s, 1H), 3.32 - 3.29 (m, 4H), 3.10 - 3.06 (m, 4H), 1.16 (s, 3H), 0.74 - 0.71 (m, 2H), 0.47 - 0.44 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 470 [M+H] ⁺ .
Example 342	 (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(hydroxymethyl)morpholin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.82 (s, 1H), 7.89 (s, 1H), 7.26 (t, <i>J</i> = 53.5 Hz, 1H), 6.73 (s, 1H), 4.11 - 4.06 (m, 1H), 3.97 - 3.91 (m, 1H), 3.88 - 3.83 (m, 1H), 3.73 - 3.66 (m, 3H), 3.64 - 3.60 (m, 1H), 3.03 (dd, <i>J</i> = 11.6, 8.6 Hz, 1H), 2.85 (dd, <i>J</i> = 11.8, 10.3 Hz, 1H), 1.25 (s, 3H), 0.85 - 0.81 (m, 2H), 0.52 - 0.48 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 501 [M+H] ⁺ .
Example 343	 N-(1-methylcyclopropyl)-8-(4-(4-oxoazetidine-2-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 8.12 (s, 1H), 6.73 (s, 1H), 4.54 - 4.46 (m, 1H), 3.81 - 3.73 (m, 2H), 3.71 - 3.57 (m, 2H), 3.34 - 3.30 (m, 4H), 3.28 - 3.22 (m, 1H), 2.99 - 2.90 (m, 1H), 1.16 (s, 3H), 0.77 - 0.69 (m, 2H), 0.49 - 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 585 [M+H] ⁺ .

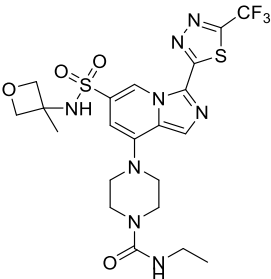
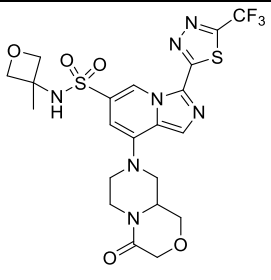
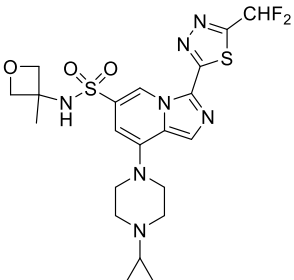
Example 344	 N-(1-cyanocyclopropyl)-8-(4-isobutryl-2-methylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, MeOD) δ 9.89 (s, 1H), 7.97 (s, 1H), 6.79 (s, 1H), 4.65 – 4.44 (m, 1H), 4.30 – 4.13 (m, 2H), 3.99 – 3.79 (m, 1H), 3.62 – 3.55 (m, 1H), 3.51 – 3.44 (m, 1H), 3.29 – 3.22 (m, 1H), 3.11 – 2.98 (m, 1H), 1.60 – 1.54 (m, 1H), 1.50 – 1.43 (m, 2H), 1.24 – 1.18 (m, 2H), 1.18 – 1.11 (m, 6H), 1.11 – 0.99 (m, 2H). LC/MS (ESI) (m/z): 583 [M+H]⁺.
Example 345	 8-(4-(1-(hydroxymethyl)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), 8.46 (s, 1H), 8.12 (s, 1H), 6.73 (s, 1H), 4.97 – 4.89 (m, 1H), 3.99 – 3.71 (m, 4H), 3.54 – 3.47 (m, 2H), 3.31 – 3.25 (m, 4H), 1.16 (s, 3H), 0.83 – 0.77 (m, 2H), 0.75 – 0.68 (m, 4H), 0.50 – 0.41 (m, 2H). LC/MS (ESI) (m/z): 586 [M+H]⁺.
Example 346	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxy-4-(methoxymethyl)piperidin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.56 (s, 1H), 8.42 (s, 1H), 7.97 (s, 1H), 7.68 (t, <i>J</i> = 53.2 Hz, 1H), 6.69 (s, 1H), 4.58 (s, 1H), 3.53 (d, <i>J</i> = 12.1 Hz, 2H), 3.30 – 3.23 (m, 5H), 3.22 – 3.17 (m, 2H), 1.91 – 1.83 (m, 2H), 1.62 – 1.57 (m, 2H), 1.15 (s, 3H), 0.72 (t, <i>J</i> = 5.5 Hz, 2H), 0.45 (q, <i>J</i> = 4.9 Hz, 2H). LC/MS (ESI) (m/z): 529 [M+H]⁺.
Example 347		¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.61 (s, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.69 (s, 1H), 3.90 – 3.84 (m, 4H), 3.30 – 3.25 (m, 4H), 1.15 (s, 3H), 0.76 – 0.69 (m, 2H), 0.48 – 0.42 (m, 2H). LC/MS (ESI) (m/z):

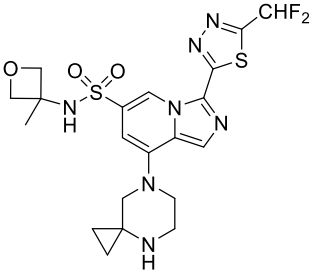
	3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-morpholinoimidazo[1,5-a]pyridine-6-sulfonamide	471 [M+H].
Example 348	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-hydroxy-3-methoxypiperidin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.56 (s, 1H), 8.42 (s, 1H), 7.96 (s, 1H), 7.68 (t, <i>J</i> = 53.1 Hz, 1H), 6.68 (s, 1H), 5.16 – 5.02 (m, 1H), 3.80 – 3.65 (m, 1H), 3.64 – 3.46 (m, 2H), 3.39 (s, 3H), 3.28 – 3.20 (m, 1H), 3.19 – 2.83 (m, 2H), 2.08 – 1.94 (m, 1H), 1.81 – 1.56 (m, 1H), 1.15 (s, 3H), 0.78 – 0.70 (m, 2H), 0.49 – 0.43 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 515 [M+H] ⁺ .
Example 349	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3,4-dihydroxypiperidin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.54 (s, 1H), 8.43 (s, 1H), 7.96 (s, 1H), 7.68 (s, 1H), 6.67 (s, 1H), 4.79 (d, <i>J</i> = 4.8 Hz, 1H), 4.65 (d, <i>J</i> = 4.2 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.46 – 3.33 (m, 2H), 3.27 – 3.25 (m, 2H), 1.86 – 1.81 (m, 2H), 1.15 (s, 3H), 0.73 – 0.70 (m, 2H), 0.46 – 0.42 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 501 [M+H] ⁺ .
Example 350	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-((1-methoxycyclopropyl)methyl)piperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.69 (t, <i>J</i> = 53.1 Hz, 1H), 6.77 (s, 1H), 3.96 – 3.86 (m, 2H), 3.81 – 3.75 (m, 2H), 3.50 – 3.41 (m, 4H), 3.37 – 3.31 (m, 2H), 3.30 (s, 3H), 1.18 (s, 3H), 1.01 – 0.95 (m, 2H), 0.84 – 0.78 (m, 2H), 0.76 – 0.71 (m, 2H), 0.50 – 0.44 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 554 [M+H] ⁺ .

Example 351	 8-(4-(3,3-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.81 (s, 1H), 7.96 (s, 1H), 6.79 - 6.73 (m, 1H), 4.10 - 3.95 (m, 3H), 3.89 - 3.77 (m, 2H), 3.50 - 3.43 (m, 2H), 3.38 - 3.32 (m, 2H), 3.24 - 3.18 (m, 1H), 2.62 - 2.54 (m, 1H), 2.42 - 2.34 (m, 5H), 1.26 (s, 3H), 0.85 - 0.81 (m, 2H), 0.52 - 0.49 (m, 2H). LC/MS (ESI) (m/z): 635 [M+H]⁺.
Example 352	 (R)-8-(4-(4,4-difluoropyrrolidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (s, 1H), 8.46 (s, 1H), 8.12 (s, 1H), 6.72 (s, 1H), 4.32 - 4.26 (m, 1H), 3.85 - 3.79 (m, 2H), 3.75 - 3.69 (m, 2H), 3.31 - 3.19 (m, 6H), 3.06 - 2.98 (m, 1H), 2.48 - 2.28 (m, 2H), 1.16 (s, 3H), 0.74 - 0.70 (m, 2H), 0.47 - 0.44 (m, 2H). LC/MS (ESI) (m/z): 621 [M+H]⁺
Example 353	 (R)-8-(4-(4,4-difluoro-1-methylpyrrolidine-2-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.80 (s, 1H), 7.94 (d, <i>J</i> = 1.5 Hz, 1H), 6.75 (s, 1H), 3.97 - 3.88 (m, 4H), 3.76 - 3.72 (m, 1H), 3.45 - 3.36 (m, 4H), 2.80 - 2.68 (m, 2H), 2.44 - 2.16 (m, 5H), 1.27 - 1.24 (m, 3H), 0.84 - 0.80 (m, 2H), 0.52 - 0.48 (m, 2H). LC/MS (ESI) (m/z): 635 [M+H]⁺

Example 354	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6S)-2,6-dimethylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.57 (s, 1H), 8.71 (s, 1H), 7.94 (s, 1H), 7.74 (t, <i>J</i> = 53.2 Hz, 1H), 6.68 (s, 1H), 4.63 (t, <i>J</i> = 6.6 Hz, 2H), 4.25 - 4.13 (m, 6H), 3.14 - 3.10 (m, 2H), 1.50 (s, 3H), 1.31 (d, <i>J</i> = 6.3 Hz, 6H). LC/MS (ESI) (m/z): 515 [M+H]⁺.
Example 355	 8-((2S,6S)-2,6-dimethylmorpholino)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CDCl₃) δ 9.80 (s, 1H), 7.65 (s, 1H), 6.57 (s, 1H), 4.74 (d, <i>J</i> = 5.4 Hz, 2H), 4.37 (d, <i>J</i> = 6.8 Hz, 2H), 4.22 - 4.18 (m, 2H), 3.26 - 3.22 (m, 2H), 3.11 - 3.06 (m, 2H), 1.68 (s, 3H), 1.35 (d, <i>J</i> = 6.4 Hz, 6H). LC/MS (ESI) (m/z): 533 [M+H]⁺.
Example 356	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-(fluoromethyl)oxetan-3-yl)-8-(3-(methoxymethyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.57 (s, 1H), 7.97 (s, 1H), 7.67 (t, <i>J</i> = 53.1 Hz, 1H), 6.71 (s, 1H), 4.72 (s, 1H), 4.65 - 4.62 (m, 2H), 4.60 (s, 1H), 4.38 (d, <i>J</i> = 6.8 Hz, 2H), 3.64 - 3.54 (m, 1H), 3.45 - 3.41 (m, 2H), 3.31 (s, 3H), 3.13 - 3.05 (m, 3H), 3.00 - 2.95 (m, 1H), 2.90 - 2.85 (m, 1H), 2.76 - 2.70 (m, 1H). LC/MS (ESI) (m/z): 548 [M+H]⁺.
Example 357	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(methoxymethyl)piperazin-1-yl)-N-(3-(methoxymethyl)oxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.85 (s, 1H), 7.92 (s, 1H), 7.46 - 7.20 (m, 1H), 6.81 (d, <i>J</i> = 1.1 Hz, 1H), 4.79 (d, <i>J</i> = 6.3 Hz, 2H), 4.32 (d, <i>J</i> = 6.7 Hz, 2H), 3.93 - 3.77 (m, 2H), 3.73 - 3.61 (m, 3H), 3.50 - 3.38 (m, 2H), 3.49 (s, 3H), 3.23 - 3.09 (m, 2H), 1.64 (s, 3H). LC/MS (ESI) (m/z): 530 [M+H]⁺.

	-N-(3-methyloxetan-3-yl)imidazo[1,5-a] pyridine-6-sulfonamide	
Example 358	 8-(3-(methoxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.86 (s, 1H), 7.99 (s, 1H), 6.87 (s, 1H), 4.85 - 4.79 (m, 2H), 4.33 (d, <i>J</i> = 6.6 Hz, 2H), 3.90 - 3.86 (m, 2H), 3.87 - 3.84 (m, 1H), 3.79 - 3.75 (m, 1H), 3.71 - 3.67 (m, 1H), 3.59 - 3.52 (m, 2H), 3.49 (s, 3H), 3.27 - 3.21 (m, 2H), 1.65 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 548 [M+H] ⁺ .
Example 359	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-(fluoromethyl)oxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.57 (s, 1H), 7.90 (s, 1H), 7.67 (t, <i>J</i> = 53.4 Hz, 1H), 6.71 (s, 1H), 4.72 (s, 1H), 4.66 - 4.60 (m, 3H), 4.38 (d, <i>J</i> = 6.6 Hz, 2H), 3.08 - 3.04 (m, 6H), 1.23 (d, <i>J</i> = 6.4 Hz, 6H). LC/MS (ESI) (<i>m/z</i>): 532 [M+H] ⁺ .
Example 360	 8-(3-(methoxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.90 (s, 1H), 8.50 (s, 1H), 7.15 (s, 1H), 4.78 (d, <i>J</i> = 6.2 Hz, 2H), 4.41 - 4.17 (m, 4H), 3.67 - 3.50 (m, 3H), 3.44 (s, 3H), 3.40 - 3.33 (m, 2H), 3.16 - 3.09 (m, 1H), 3.06 - 2.96 (m, 1H), 1.63 (s, 3H). LC/MS (ESI) (<i>m/z</i>): 548 [M+H] ⁺ .
Example 361		¹ H NMR (400 MHz, CD ₃ OD) δ 9.88 (s, 1H), 7.96 (s, 1H), 7.34 (t, <i>J</i> = 53.5 Hz, 1H), 6.84 (s, 1H), 4.80 - 4.77 (m, 2H), 4.36 - 4.31 (m, 2H), 3.98 - 3.82 (m, 4H), 3.77 - 3.70 (m, 2H), 3.59 - 3.51 (m, 2H), 3.28 - 3.17 (m, 2H), 1.65 (s,

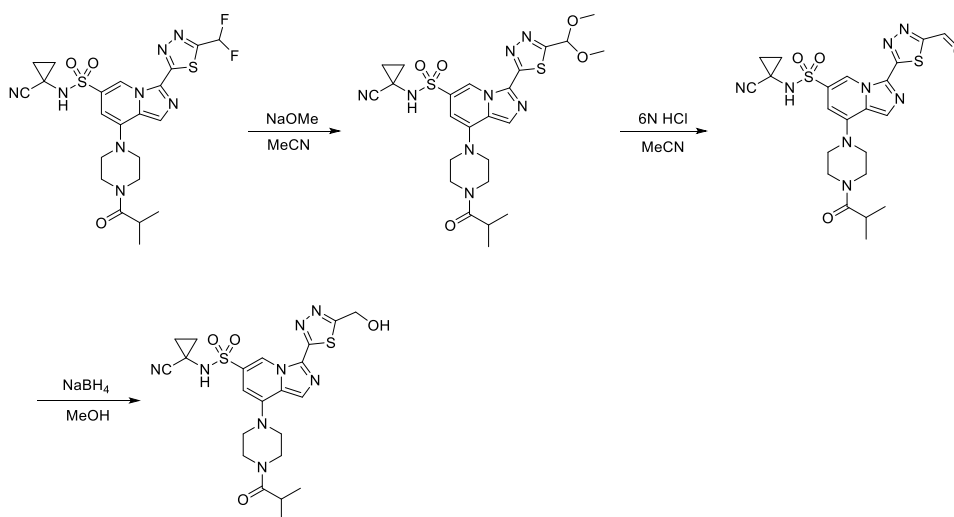
	3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(isopropoxymethyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	3H), 1.25 (d, $J = 6.1$ Hz, 6H). LC/MS (ESI) (m/z): 558 [M+H] ⁺ .
Example 362	 N-ethyl-4-(6-(N-(3-methyloxetan-3-yl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperazine-1-carboxamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.80 (s, 1H), 7.93 (s, 1H), 6.78 (s, 1H), 4.79 (d, $J = 6.3$ Hz, 2H), 4.31 (d, $J = 6.4$ Hz, 2H), 3.69 - 3.65 (m, 4H), 3.39 - 3.36 (m, 4H), 3.26 - 3.21 (m, 2H), 1.64 (s, 3H), 1.16 - 1.12 (m, 3H). LC/MS (ESI) (m/z): 575 [M+H] ⁺ .
Example 363	 N-(3-methyloxetan-3-yl)-8-(4-oxohexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.82 (s, 1H), 7.99 (s, 1H), 6.82 (s, 1H), 4.81 (d, $J = 6.3$ Hz, 2H), 4.59 - 4.58 (m, 2H), 4.32 (d, $J = 6.3$ Hz, 2H), 4.20 - 4.19 (m, 2H), 4.03 - 3.98 (m, 1H), 3.88 - 3.71 (m, 4H), 3.20 - 3.15 (m, 1H), 2.98 - 2.91 (m, 1H), 1.64 (s, 3H). LC/MS (ESI) (m/z): 574 [M+H] ⁺ .
Example 364	 8-(4-cyclopropylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.81 (s, 1H), 7.88 (s, 1H), 7.33 (t, $J = 53.6$ Hz, 1H), 6.73 (s, 1H), 4.79 (d, $J = 5.8$ Hz, 2H), 4.31 (d, $J = 5.2$ Hz, 2H), 3.38 - 3.35 (m, 4H), 2.95 - 2.92 (m, 4H), 1.86 - 1.81 (m, 1H), 1.63 (s, 3H), 0.58 - 0.49 (m, 4H). LC/MS (ESI) (m/z): 526 [M+H] ⁺ .

Example 365	 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(4,7-diazaspiro[2.5]octan-7-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, CD₃OD) δ 9.83 (s, 1H), 7.82 (s, 1H), 7.33 (t, <i>J</i> = 53.5 Hz, 1H), 6.75 (s, 1H), 4.81 - 4.78 (m, 2H), 4.33 - 4.30 (m, 2H), 3.52 - 3.48 (m, 2H), 3.38 - 3.34 (m, 2H), 3.33 - 3.32 (m, 2H), 1.64 (s, 3H), 0.92 - 0.87 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 512 [M+H]⁺.
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Example

366:

N-(1-cyanocyclopropyl)-3-(5-(hydroxymethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

N-(1-cyanocyclopropyl)-3-(5-(dimethoxymethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, 5M sodium methoxide/methanol solution (1 mL) was slowly added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide (230 mg, 0.418 mmol) in acetonitrile (3 mL). The reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate twice. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 170 mg, yield: 70.8%), which was directly used in the next step of reaction without purification. LC/MS (ESI) *m/z*: 575 [M+H]⁺.

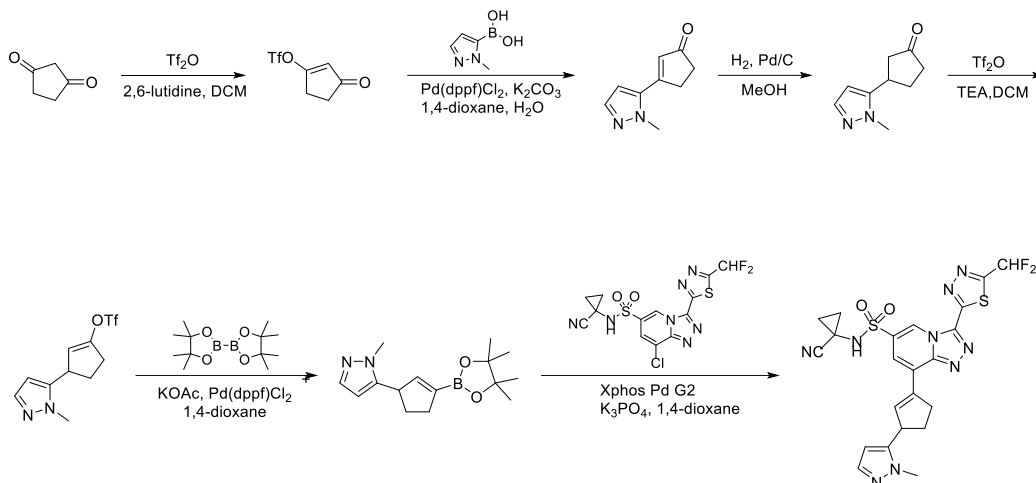
Step**2:****N-(1-cyanocyclopropyl)-3-(5-formyl-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide**

At 0°C, 6N hydrochloric acid solution (0.5 mL) was slowly added to the solution of N-(1-cyanocyclopropyl)-3-(5-(dimethoxymethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide (35 mg, 0.061 mmol) in acetonitrile (1.5 mL). The reaction mixture was stirred at 70 °C for 3 hour. After completion of the reaction, the reaction mixture was diluted with water, and extracted with chloroform/isopropanol (3:1). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 28 mg, yield: 87.0%), which was directly used in the next step of reaction without purification. LC/MS (ESI) m/z: 529 [M+H]⁺.

Step**3:****N-(1-cyanocyclopropyl)-3-(5-(hydroxymethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide**

At 0°C, sodium borohydride (3 mg, 0.08 mmol) was slowly added to the solution of N-(1-cyanocyclopropyl)-3-(5-formyl-1,3,4-thiadiazol-2-yl)-8-(4-isobutyrylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide (28 mg, 0.053 mmol) in methanol (1 mL). The mixture was stirred at room temperature for 30 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution, and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 7 mg, yield: 24.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.71 (s, 1H), 9.47 (s, 1H), 8.01 (s, 1H), 6.61 (s, 1H), 6.38 (s, 1H), 4.95 (d, *J* = 4.1 Hz, 2H), 3.81-3.70 (m, 4H), 3.32-3.27 (m, 4H), 2.99-2.90 (m, 1H), 1.52-1.43 (m, 2H), 1.40-1.35 (m, 2H), 1.05 (d, *J* = 6.4 Hz, 6H). LC/MS (ESI) m/z: 531 [M+H]⁺.

Example**367:****N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(1-methyl-1H-pyrazol-5-yl)cyclopent-1-en-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide**



Step 1: 3-oxocyclopent-1-en-1-yl trifluoromethanesulfonate

- of nitrogen at 70°C, trifluoromethanesulfonic anhydride (1 g, 3.67 mmol) was dropwise added slowly to the solution of cyclopentan-1,3-diketone (300 mg, 3.06 mmol) and 2,6-dimethylpyridine (200 mg, 4.59 mmol) in dichloromethane (10 mL); and the mixture was stirred at -70°C Under an atmosphere for one hour. The reaction mixture was quenched with ice water and extracted with dichloromethane twice. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-40% ethyl acetate) to obtain the title compound (yellow oil, 600 mg, yield: 85.2%). LC/MS (ESI) (m/z): 231 [M+H]⁺.

Step 2: 3-(1-methyl-1H-pyrazol-5-yl)cyclopent-2-en-1-one

Under an atmosphere of nitrogen, 1-methyl-1H-pyrazol-5-boric acid (126 mg, 1.0 mmol), potassium carbonate (414 mg, 3.0 mmol), and Pd(dppf)Cl₂ (73 mg, 0.1 mmol) were sequentially added to the solution of 3-oxocyclopent-1-en-1-yl trifluoromethanesulfonate (230 mg, 1.0 mmol) in 1,4-dioxane (4 mL) and water (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 2 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate, and sequentially washed with water and saturated brine; and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified and separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (white solid, 140 mg, yield: 85.8%). LC/MS (ESI) (m/z): 163 [M+H]⁺.

Step 3: 3-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one

Under an atmosphere of nitrogen, Pd/C (20 mg) with the mass fraction of 10% was added to the solution of 3-(1-methyl-1H-pyrazol-5-yl)cyclopent-2-en-1-one (140 mg, 0.86 mmol) in methanol (5 mL); the flask was replaced with nitrogen gas three times and then the mixture was stirred at room temperature for 6 hours under an atmosphere of hydrogen. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (white solid, 145 mg, yield:

100%). LC/MS (ESI) (m/z): 165 [M+H]⁺.

Step 4: 3-(1-methyl-1H-pyrazol-5-yl)cyclopent-1-en-1-yl trifluoromethanesulfonate

At -70°C, NaHMDS (4.5 mL, 4.5 mmol, 1M in THF) was dropwise added slowly to the solution of 3-(1-methyl-1H-pyrazol-5-yl)cyclopentan-1-one (500 mg, 3.03 mmol) in tetrahydrofuran (10mL); the mixture was stirred at -70°C for 0.5 hour; then, N-phenylbis(trifluorotrifluoromethanesulfon)imide (1.3 g, 3.6 mmol) in tetrahydrofuran (5 mL) was dropwise added slowly; and the reaction mixture was continued to be stirred at -70°C for 0.5 hour. The reaction mixture was quenched with ice water and extracted with ethyl acetate; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow oil, 600 mg, yield: 67.5%). LC/MS (ESI) (m/z): 297 [M+H]⁺.

Step 5: 1-methyl-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-yl)-1H-pyrazole

Under an atmosphere of nitrogen, bis(pinacolato)diboron (430 mg, 1.69 mmol), potassium acetate (497 mg, 5.1 mmol) and Pd(dppf)Cl₂ (123 mg, 0.17 mmol) were sequentially added to the solution of 3-(1-methyl-1H-pyrazol-5-yl)cyclopent-1-ene-1-yltrifluoromethanesulfonate (500 mg, 1.69 mmol) in 1,4-dioxane (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 2 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified and separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 400 mg, yield: 86.4%). LC/MS (ESI) (m/z): 275 [M+H]⁺.

Step

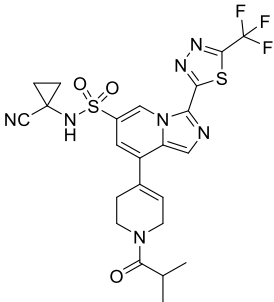
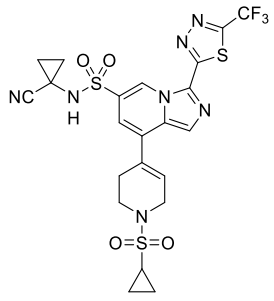
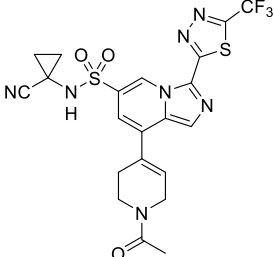
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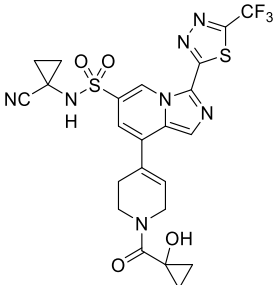
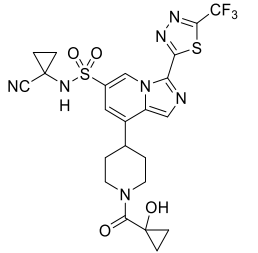
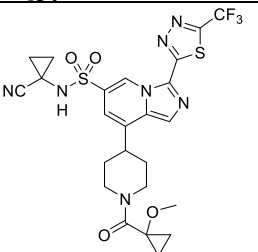
N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(1-methyl-1H-pyrazol-5-yl)cyclopent-1-en-1-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

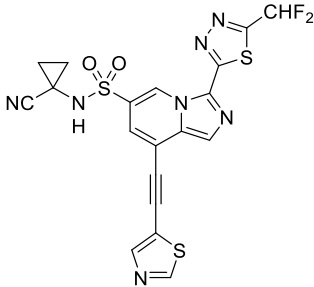
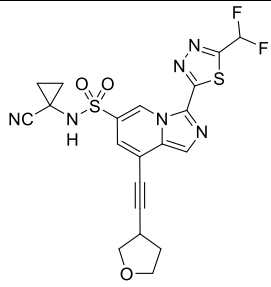
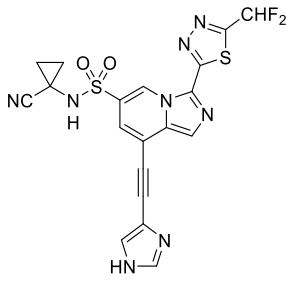
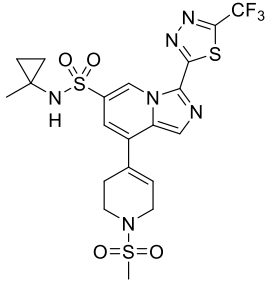
Under an atmosphere of nitrogen, 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide (80 mg, 0.18 mmol), potassium phosphate (115 mg, 0.54 mmol), Pd(dppf)Cl₂ (14 mg, 0.02 mmol) were sequentially added to the solution of 1-methyl-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxoboracyclopentan-2-yl)cyclopent-2-ene-1-yl)-1H-pyrazole (50 mg, 0.18 mmol) in 1,4-dioxane (4 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 2 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine in sequence, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 60 mg, yield: 61.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.76 (d, *J* = 1.3 Hz, 1H), 7.92-7.61 (m, 4H), 7.31 (d, *J*

= 1.6 Hz, 1H), 6.04 (d, J = 1.8 Hz, 1H), 4.51-4.44 (m, 1H), 3.87 (s, 3H), 3.12-3.04 (m, 1H), 3.02-2.96 (m, 1H), 2.69-2.60 (m, 1H), 2.02-1.94 (m, 1H), 1.50-1.47 (m, 2H), 1.39-1.36 (m, 2H). LC/MS (ESI) (m/z): 544 $[M+H]^+$.

By referring to the preparation method in Example 367, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

Example	Structure and name	Analysis data
Example 368	 N-(1-cyanocyclopropyl)-8-(1-isobutyryl-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.93 (s, 1H), 9.59 (s, 1H), 8.24 (s, 1H), 7.35 (s, 1H), 6.55 (d, J = 11.4 Hz, 1H), 4.39 - 4.22 (m, 2H), 3.82 - 3.75 (m, 2H), 3.04 - 2.94 (m, 1H), 2.71 - 2.67 (m, 1H), 2.62 - 2.56 (m, 1H), 1.53 - 1.48 (m, 2H), 1.43 - 1.38 (m, 2H), 1.07 (d, J = 6.2 Hz, 6H). LC/MS (ESI) m/z : 566 $[M+H]^+$.
Example 369	 N-(1-cyanocyclopropyl)-8-(1-(cyclopropylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.94 (s, 1H), 9.60 (s, 1H), 8.25 (s, 1H), 7.36 (s, 1H), 6.56 (s, 1H), 4.13 - 4.03 (m, 2H), 3.60 - 3.52 (m, 2H), 2.76 - 2.73 (m, 2H), 1.53 - 1.47 (m, 2H), 1.43 - 1.36 (m, 2H), 1.27 - 1.20 (m, 1H), 1.06 - 0.99 (m, 4H). LC/MS (ESI) (m/z): 600 $[M+H]^+$.
Example 370	 8-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.91 (s, 1H), 8.20 (d, J = 6.1 Hz, 1H), 7.32 (s, 1H), 6.51 (s, 1H), 4.33 - 4.18 (m, 2H), 3.77 - 3.69 (m, 2H), 2.70 - 2.65 (m, 1H), 2.61 - 2.54 (m, 1H), 2.12 - 2.05 (m, 3H), 1.51 - 1.43 (m, 2H), 1.40 - 1.32 (m, 2H). LC/MS (ESI) (m/z): 538 $[M+H]^+$.

	N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	
Example 371	 N-(1-cyanocyclopropyl)-8-(1-(1-hydroxycyclopropane-1-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.92 (s, 1H), 8.21 (s, 1H), 7.34 (s, 1H), 6.58 (s, 1H), 6.42 (s, 1H), 4.73 – 4.15 (m, 2H), 4.11 – 3.66 (m, 2H), 2.73 – 2.55 (m, 2H), 1.56 – 1.45 (m, 2H), 1.41 – 1.31 (m, 2H), 1.04 – 0.92 (m, 2H), 0.87 – 0.76 (m, 2H). LC/MS (ESI) (m/z): 580 [M+H] ⁺ .
Example 372	 N-(1-cyanocyclopropyl)-8-(1-(1-hydroxycyclopropane-1-carbonyl)piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.87 (s, 1H), 9.57 (s, 1H), 8.29 (s, 1H), 7.28 (s, 1H), 6.38 (s, 1H), 4.66 – 4.56 (m, 1H), 3.49 – 3.48 (m, 1H), 3.23 – 3.18 (m, 2H), 2.02 (d, <i>J</i> = 12.4 Hz, 2H), 1.88 – 1.58 (m, 3H), 1.50 – 1.46 (m, 2H), 1.41 – 1.37 (m, 2H), 0.99 – 0.94 (m, 2H), 0.82 – 0.78 (m, 2H). LC/MS (ESI) (m/z): 582 [M+H] ⁺
Example 373	 N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.20 (s, 1H), 7.86 (s, 1H), 7.28 (s, 1H), 6.31 (s, 1H), 4.81 (d, <i>J</i> = 12.0 Hz, 2H), 3.37 (s, 3H), 3.33 – 3.13 (m, 2H), 3.06 – 2.81 (m, 1H), 2.16 (d, <i>J</i> = 12.7 Hz, 2H), 1.91 – 1.78 (m, 2H), 1.74 – 1.67 (m, 2H), 1.54 – 1.46 (m, 2H), 1.17 – 1.11 (m, 2H), 1.02 – 0.94 (m, 2H). LC/MS (ESI) (m/z): 596 [M+H] ⁺

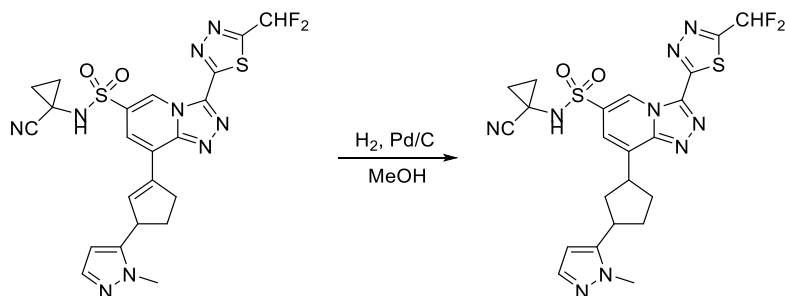
Example 374	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(thiazol-5-ylethynyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.99 (s, 1H), 9.64 (s, 1H), 9.32 (s, 1H), 8.52 (s, 1H), 8.21 (s, 1H), 7.78 (t, <i>J</i> = 53.2 Hz, 1H), 7.65 (s, 1H), 1.53 - 1.50 (m, 2H), 1.43 - 1.39 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 504 [M+H]⁺.
Example 375	 N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((tetrahydrofuran-3-yl)ethynyl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.93 (s, 1H), 9.59 (s, 1H), 8.01 (s, 1H), 7.70 (t, <i>J</i> = 53.1 Hz, 1H), 7.43 (d, <i>J</i> = 1.0 Hz, 1H), 4.07 - 4.01 (m, 1H), 3.95 - 3.88 (m, 1H), 3.85 - 3.76 (m, 2H), 3.52 - 3.45 (m, 1H), 2.41 - 2.31 (m, 1H), 2.16 - 2.08 (m, 1H), 1.55 - 1.48 (m, 2H), 1.42 - 1.35 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 491 [M+H]⁺.
Example 376	 8-((1H-imidazol-4-yl)ethynyl)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.94 (s, 1H), 9.63 (s, 1H), 8.08 - 7.55 (m, 4H), 7.50 (d, <i>J</i> = 1.3 Hz, 1H), 1.54 - 1.48 (m, 2H), 1.43 - 1.36 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 487 [M+H]⁺.
Example 377	 N-(1-methylcyclopropyl)-8-(1-(methylsulfonyl)pyridin-4-ylethynyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.84 (s, 1H), 8.52 (s, 1H), 8.21 (s, 1H), 7.36 (s, 1H), 6.54 (s, 1H), 4.05 - 3.94 (m, 2H), 3.53 - 3.47 (m, 2H), 3.05 (s, 3H), 2.77 - 2.69 (m, 2H), 1.17 (s, 3H), 0.77 - 0.67 (m, 2H), 0.52 - 0.40 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 563 [M+H]⁺.

	nyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide	
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Example

378:

N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(1-methyl-1H-pyrazol-5-yl)cyclopent-1-en-1-yl)[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

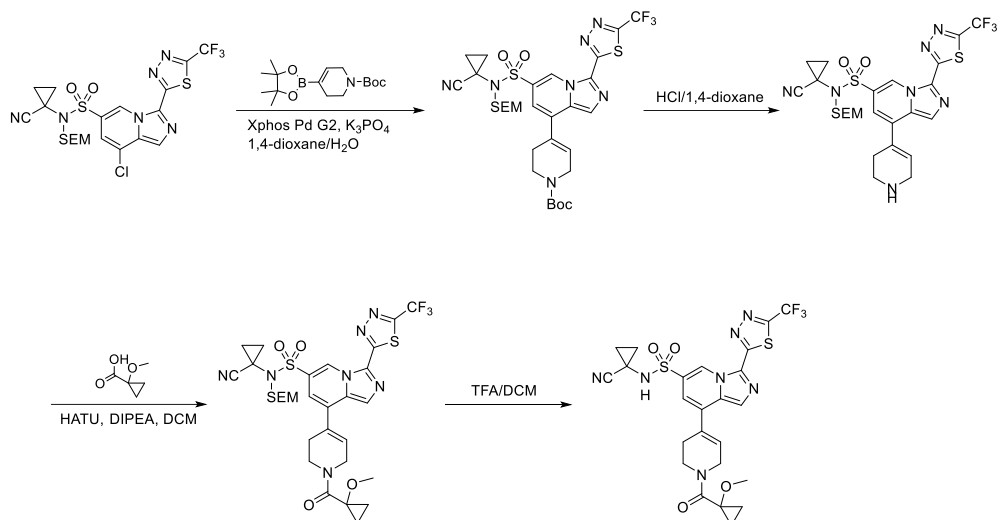


Under an atmosphere of nitrogen, Pd/C (10 mg) with the mass fraction of 10% was added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-(1-methyl-1H-pyrazol-5-yl)cyclopent-1-en-1-yl)[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide (50 mg, 0.09 mmol) in methanol (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred for 2 hours at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (white solid, 8 mg, yield: 16.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.71 (s, 1H), 7.75 (dd, *J* = 60.3, 45.8 Hz, 2H), 7.30 (d, *J* = 1.7 Hz, 1H), 6.16 (d, *J* = 1.8 Hz, 1H), 4.01 - 3.87 (m, 1H), 3.81 (s, 3H), 3.53 - 3.46 (m, 1H), 2.66 - 2.59 (m, 1H), 2.34 - 2.31 (m, 1H), 2.04 - 1.95 (m, 4H), 1.48 - 1.44 (m, 2H), 1.38 - 1.31 (m, 2H). LC/MS (ESI) (*m/z*): 546 [M+H]⁺.

Example

379:

N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Tert-butyl

4-(6-(N-(1-cyanocyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)-3,6-dihydropyridine-1(2H)-carboxylate

Under an atmosphere of nitrogen at room temperature, potassium phosphate (220 mg, 1.04 mmol) and Xphos Pd G2 (4 mg, 0.005 mmol) were sequentially added to the solution of 8-chloro-N-(1-cyanocyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (300 mg, 0.52 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaboron-2-yl)-3,6-dihydropyridin-1(2H)-tert-butyl carboxylate (240 mg, 0.78 mmol) in 1,4-dioxane (6 mL) and water (1 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 85°C for 16 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 330 mg, yield: 51%). LC/MS (ESI) (m/z): 726 [M+H]⁺.

Step 2:

N-(1-cyanocyclopropyl)-8-(1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, 4N hydrochloric acid/1,4-dioxane (5 mL) solution was slowly added to the solution of 4-(6-(N-(1-cyanocyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)-3,6-dihydropyridin-1(2H)-tert-butyl carboxylate (100 mg, 0.14 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, and concentrated under reduced pressure to obtain a crude title compound (yellow solid, 85 mg, yield: 98.6%), which was directly used in the next step of reaction without purification. LC/MS (ESI) (m/z): 626 [M+H]⁺.

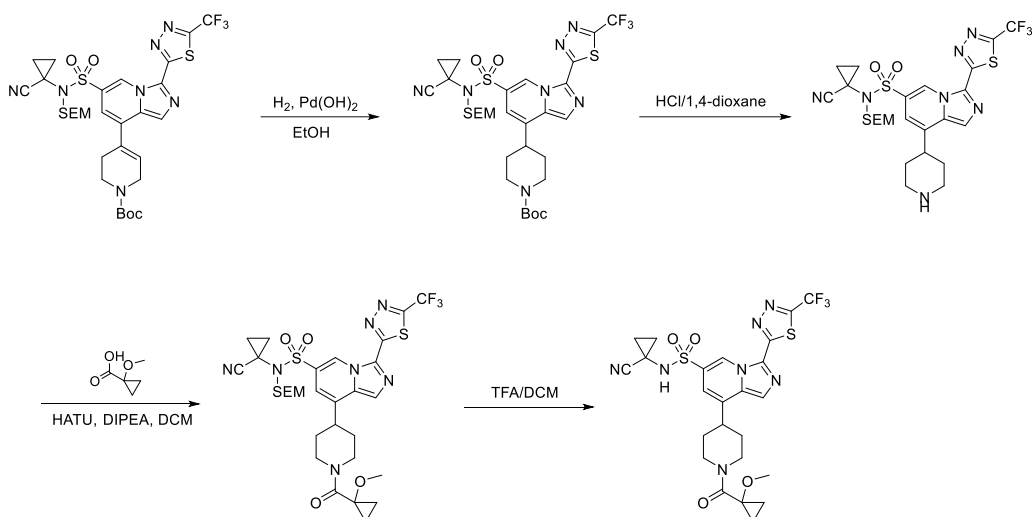
Step 3:**N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide**

At 0°C, HATU (65 mg, 0.17 mmol) and DIEA (40 mg, 0.33 mmol) were added to the solution of N-(1-cyanocyclopropyl)-8-(1,2,3,6-tetrahydropyridin-4-yl)-3-(5(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (85 mg, 0.14 mmol) and 1-hydroxycyclopropan-1-formic acid (24 mg, 0.20 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at 0°C for 1 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 70 mg, yield: 71%). LC/MS (ESI) (m/z): 724 [M+H]⁺.

Step**4:****N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide**

At 0°C, trifluoroacetic acid (0.3 mL) was dropwise added slowly to the solution of N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropan-1-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (70 mg, 0.10 mmol) in dichloromethane (1 mL). The mixture was stirred at room temperature for 30 minutes. The mixture was concentrated, and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 18 mg, yield: 31.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.94 (s, 1H), 9.58 (s, 1H), 8.23 (s, 1H), 7.36 (s, 1H), 6.60 (s, 1H), 4.65 - 4.17 (m, 2H), 4.07 - 3.72 (m, 2H), 3.27 (s, 3H), 2.68 (s, 2H), 1.58 - 1.47 (m, 2H), 1.43 - 1.35 (m, 2H), 1.07 - 1.00 (m, 2H), 0.99 - 0.91 (m, 2H). LC/MS (ESI) (m/z): 594 [M+H]⁺.

Example 380 :**N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide**



Step

1:

Tert-butyl

4-(6-(N-(1-cyanocyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperidine-1-carboxylate

Under an atmosphere of nitrogen, Pd/C (12 mg, mass fraction: 10%) was slowly added to the solution of 4-(6-(N-(1-cyanocyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)-3,6-dihydropyridin-1(2H)-tert-butyl carboxylate (270 mg, 0.37 mmol) in ethanol (5 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred for 9 hours at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (white solid, 220 mg, yield: 81.5%). LC/MS (ESI) m/z : 728 $[M+H]^+$.

Step

2:

N-(1-cyanocyclopropyl)-8-(piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, 4N hydrochloric acid/1,4-dioxane solution (5 mL) was slowly added to the solution of 4-(6-(N-(1-cyanocyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperidin-1-tert-butyl formate (220 mg, 0.30 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain a crude title compound (yellow solid, 180 mg, yield: 95.2%), which was directly used in the next step of reaction without purification LC/MS (ESI) (m/z): 628 $[M+H]^+$.

Step

3:

N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, HATU (65 mg, 0.17 mmol) and DIEA (40 mg, 0.33 mmol) were added to the solution of N-(1-cyanocyclopropyl)-8-(piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (70 mg, 0.11 mmol) and 1-hydroxycyclopropan-1-formic acid (25 mg, 0.22 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at 0°C for 1 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 40 mg, yield: 50%). LC/MS (ESI) (m/z): 726 [M+H]⁺.

Step

4:

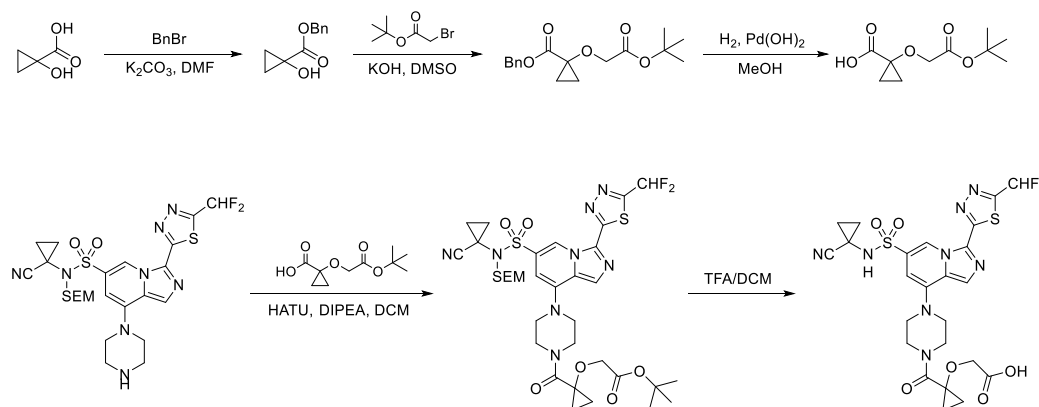
N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (0.3 mL) was added to the solution of N-(1-cyanocyclopropyl)-8-(1-(1-methoxycyclopropane-1-carbonyl)piperidin-4-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (40 mg, 0.06 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 1 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 5 mg, yield: 16%). ¹H NMR (400 MHz, CDCl₃) δ 10.20 (s, 1H), 7.86 (s, 1H), 7.28 (s, 1H), 6.31 (s, 1H), 4.81 (d, *J* = 12.0 Hz, 2H), 3.37 (s, 3H), 3.33 - 3.13 (m, 2H), 3.06 - 2.81 (m, 1H), 2.16 (d, *J* = 12.7 Hz, 2H), 1.91 - 1.78 (m, 2H), 1.74 - 1.67 (m, 2H), 1.54 - 1.46 (m, 2H), 1.17 - 1.11 (m, 2H), 1.02 - 0.94 (m, 2H). LC/MS (ESI) (m/z): 596 [M+H]⁺.

Example

381:

2-(1-(4-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperazine-1-carbonyl)cyclopropoxy)acetic acid



Step 1: Benzyl 1-hydroxycyclopropane-1-carboxylate

At 0°C, potassium carbonate (7 g, 50.7 mmol) and benzyl bromide (4 g, 23.5 mmol) were added to the solution of 1-hydroxycyclopropan-1-formic acid (2 g, 19.6 mmol) in N,N-dimethylformamide (20 mL). The reaction mixture was stirred for 3 hours at room temperature under an atmosphere of nitrogen. After completion of the reaction, the saturated ammonium chloride solution was used for quenching; and the reaction mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-10% ethyl acetate) to obtain the title compound (colorless liquid, 3 g, yield: 79.7%). ¹H NMR (400 MHz, CDCl₃) δ 7.35 - 7.21 (m, 5H), 5.10 (s, 2H), 4.04 (q, *J* = 7.1 Hz, 1H), 1.25 (dd, *J* = 8.0, 4.9 Hz, 2H), 1.09 (dd, *J* = 8.0, 4.9 Hz, 2H).

Step 2: Benzyl 1-(2-(tert-butoxy)-2-oxoethoxy)cyclopropane-1-carboxylate

At 0°C, potassium hydroxide (520 mg, 9.25 mmol) and 2-bromotert-butyl acetate (1.2 g, 6.01 mmol) were sequentially added to the solution of 1-hydroxycyclopropan-1-benzyl formate (1 g, 4.62 mmol) in dimethyl sulfoxide (10 mL). The reaction mixture was stirred at 0°C for 3 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-5% ethyl acetate) to obtain the title compound (colorless liquid, 1.2 g, yield: 84.7%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.27 (m, 5H), 5.17 (s, 2H), 4.15 (s, 2H), 1.45 (s, 9H), 1.35 - 1.28 (m, 4H).

Step 3: 1-(2-(tert-butoxy)-2-oxoethoxy)cyclopropane-1-carboxylic acid

At room temperature, palladium hydroxide on carbon (50 mg, mass fraction: 10%) were added to the solution of 1-(2-(tert-butoxy)-2-oxoethoxy)cyclopropan-1-benzyl formate (600 mg, 1.96 mmol) in methanol (8 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred for 2 hours at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (white solid, 400 mg, yield: 94.4%), which was directly used in the next step without purification. LC/MS (ESI) (*m/z*): 217 [M+H]⁺.

Step 4: Tert-butyl 2-(1-(4-(6-(N-(1-cyanocyclopropyl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperazine-1-carbonyl)cyclopropoxy)acetate

At room temperature, 1-(2-(tert-butoxy)-2-oxoethoxy)cyclopropan-1-formic acid (39 mg, 0.180 mmol), N,N-diisopropylethylamine (29 mg, 0.225 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (41 mg, 0.108 mmol) were added to the solution of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(piperazin-1-yl)-N-(2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (55 mg, 0.090 mmol) in N,N-dimethylformamide (2

mL). The reaction mixture was stirred at room temperature for 0.5 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-35% ethyl acetate) to obtain the title compound (yellow solid, 55 mg, yield: 75.5%). LC/MS (ESI) (m/z): 809 [M+H]⁺.

Step

5:

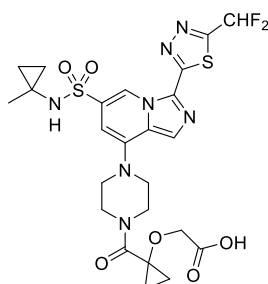
2-(1-(4-(6-(N-(1-cyanocyclopropyl)sulfamoyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperazine-1-carbonyl)cyclopropoxy)acetic acid

At 0°C, trifluoroacetic acid (1 mL) was added to the solution of 2-(1-(4-(6-(N-(1-cyanocyclopropyl)-N-((2-(trimethylmethylsilyl)ethoxy)methyl)aminosulfonyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridin-8-yl)piperazin-1-carbonyl)cyclopropoxy)tert-butyl acetate (55 mg, 0.068 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was dripped to 5% aqueous sodium bicarbonate solution cooled in the ice water bath, and extracted with dichloromethane. The organic phase was combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by pre-HPLC (C18, 10-50% acetonitrile in water containing 0.1% FA) to obtain the title compound (yellow solid, 15 mg, yield: 35.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.12 (s, 1H), 7.69 (t, *J* = 53.2 Hz, 1H), 6.68 (s, 1H), 4.05 (s, 2H), 3.98 - 3.63 (m, 4H), 3.53 - 3.37 (m, 4H), 1.50 - 1.47 (m, 2H), 1.40 - 1.36 (m, 2H), 1.07 - 1.03 (m, 4H). LC/MS (ESI) (m/z): 623 [M+H]⁺.

Example

382:

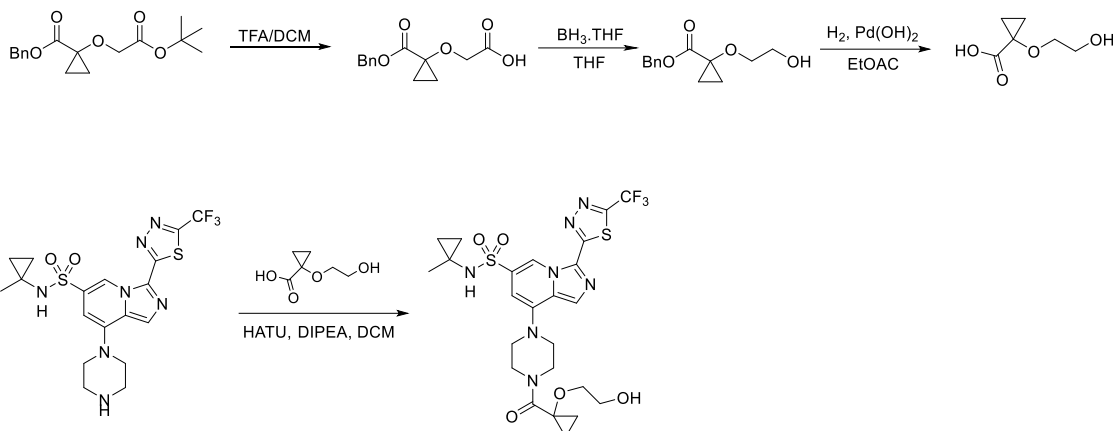
2-(1-(4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)piperazine-1-carbonyl)cyclopropoxy)acetic acid



The title compound was obtained by referring to the preparation method in **Example 381**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.61 (s, 1H), 8.44 (s, 1H), 8.09 (s, 1H), 7.69 (t, *J* = 53.1 Hz, 1H), 6.70 (s, 1H), 4.05 (s, 2H), 3.98 - 3.59 (m, 4H), 3.61 - 3.10 (m, 4H), 1.16 (s, 3H), 1.09 - 0.99 (m, 4H), 0.80 - 0.68 (m, 2H), 0.52 - 0.40 (m, 2H). LC/MS (ESI) (m/z): 612 [M+H]⁺.

Example 383:

8-(4-(1-(2-hydroxyethoxy)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: 2-(1-((benzyloxy)carbonyl)cyclopropoxy)acetic acid

At 0°C, trifluoroacetic acid (4.5 mL) was added to the solution of 1-(2-(tert-butoxy)-2-oxoethoxy)cyclopropan-1-benzyl formate (1.8 g, 5.87 mmol) in dichloromethane (9 mL). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (yellow liquid, 1.5 g, yield: 100%). LC/MS (ESI) (m/z): 251 [M+H]⁺.

Step 2: Benzyl 1-(2-(hydroxyethoxy)cyclopropane-1-carboxylate

At 0°C, borane tetrahydrofuran (11.7 mL, 11.7 mmol, 1M) solution was dropwise added slowly to the solution of 2-(1-(benzyloxy)carbonyl)cyclopropoxy)acetic acid (1.5 g, 5.87 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred at 65°C for one hour. After completion of the reaction, the reaction mixture was quenched by dropwise adding methanol in an ice water bath. The reaction mixture was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-15% ethyl acetate) to obtain the title compound (colorless liquid, 900 mg, yield: 64.8%). LC/MS (ESI) (m/z): 237 [M+H]⁺.

Step 3: 1-(2-(hydroxyethoxy)cyclopropane-1-carboxylic acid

At room temperature, palladium hydroxide (10 mg, mass fraction: 10%) was added to the solution of 1-(2-(hydroxyethoxy)cyclopropan-1-benzyl formate (50 mg, 2.12 mmol) in ethyl acetate (2 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred for 2 hours at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (colorless liquid, 30 mg, yield: 97.0%), which was directly used in the next step without purification. LC/MS (ESI) (m/z): 147 [M+H]⁺.

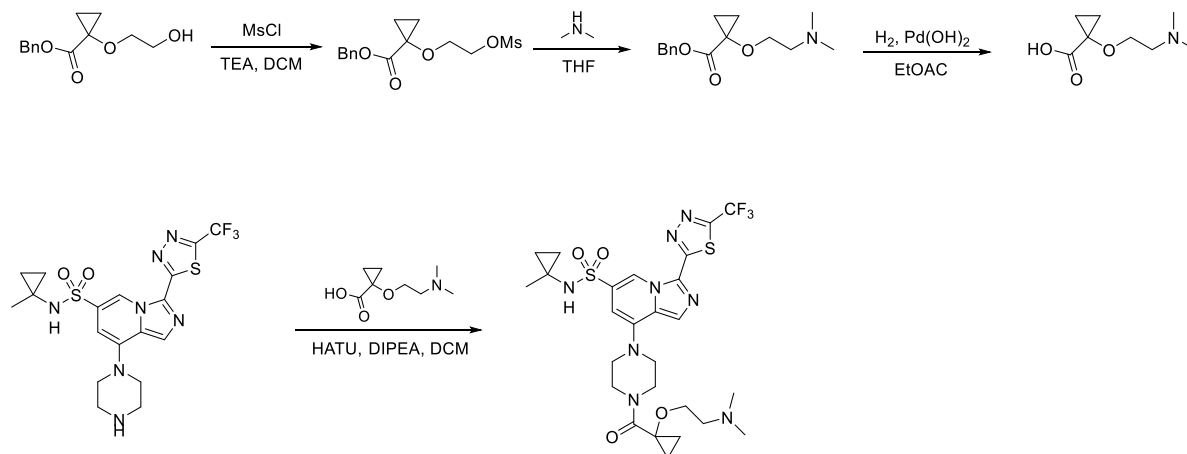
Step

4:

8-(4-(1-(2-hydroxyethoxy)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifl

uoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, 1-(2-hydroxyethoxy)cyclopropan-1-formic acid (23 mg, 0.206 mmol), N,N-diisopropylethylamine (33 mg, 0.256 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (47 mg, 0.123 mmol) were added to the solution of N-(1-methylcyclopropyl)-8-(piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (50 mg, 0.103 mmol) in N,N-dimethylformamide (2 mL). The reaction mixture was stirred at room temperature for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by pre-HPLC (C18, 10-50% acetonitrile in water containing 0.1% FA) to obtain the title compound (yellow solid, 16 mg, yield: 25.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.58 (s, 1H), 8.45 (s, 1H), 8.13 (s, 1H), 6.73 (s, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 4.18 - 3.65 (m, 4H), 3.51 - 3.45 (m, 4H), 3.43 - 3.33 (m, 4H), 1.16 (s, 3H), 1.08 - 1.00 (m, 2H), 0.98 - 0.90 (m, 2H), 0.77 - 0.69 (m, 2H), 0.49 - 0.41 (m, 2H). LC/MS (ESI) (*m/z*): 616 [M+H]⁺.

Example**384:****8-(4-(1-(2-(dimethylamino)ethoxy)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide****Step 1: Benzyl 1-(2-((methylsulfonyl)oxy)ethoxy)cyclopropane-1-carboxylate**

At 0°C, triethylamine (684 mg, 6.77 mmol) and methylsulfonyl chloride (503 mg, 4.39 mmol) were added to the solution of 1-(2-hydroxyethoxy)cyclopropan-1-benzyl formate (800 mg, 3.38 mmol) in dichloromethane (8 mL). The reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (colorless liquid, 888 mg, yield: 83.5%), which was directly used in the next step without purification. LC/MS (ESI) (*m/z*): 315 [M+H]⁺.

Step 2: Benzyl 1-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxylate

At 0°C, the solution of 2M dimethylamine in tetrahydrofuran (5.6 mL, 5.64 mmol) was added to the solution of 1-(2-((methylsulfonyl)oxy)ethoxy)cyclopropan-1-benzyl formate (888 mg, 2.82 mmol) in tetrahydrofuran (5 mL). The reaction mixture was allowed to react under a sealed condition at 65°C for 3 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-8% methanol) to obtain the title compound (colorless liquid, 500 mg, yield: 67.2%). LC/MS (ESI) (m/z): 264 [M+H]⁺.

Step 3: 1-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxylic acid

At room temperature, palladium hydroxide (20 mg, mass fraction: 10%) was added to the solution of 1-(2-(dimethylamino)ethoxy)cyclopropan-1-benzyl formate (150 mg, 0.570 mmol) in ethyl acetate (3 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred for 2 hours at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure to obtain the title compound (colorless liquid, 90 mg, yield: 91.2%), which was directly used in the next step without purification. LC/MS (ESI) (m/z): 174 [M+H]⁺.

Step

4:

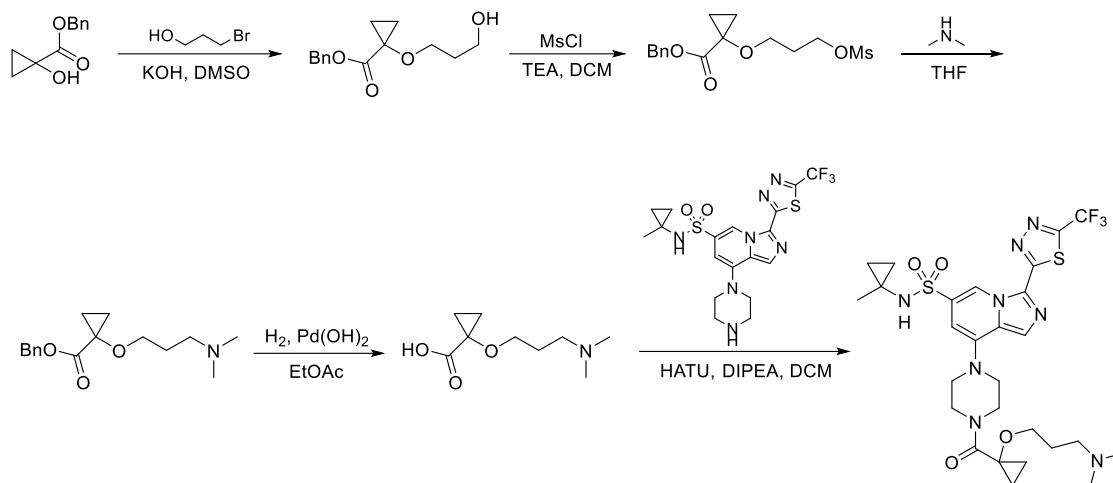
8-(4-(1-(2-(dimethylamino)ethoxy)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, 1-(2-(dimethylamino)ethoxy)cyclopropan-1-formic acid (39 mg, 0.266 mmol), N,N-diisopropylethylamine (36 mg, 0.282 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (51 mg, 0.135 mmol) were sequentially added to the solution of N-(1-methylcyclopropyl)-8-(piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (55 mg, 0.133 mmol) in N,N-dimethylformamide (2 mL). The reaction mixture was stirred at room temperature for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by pre-HPLC (C18, 10-50% acetonitrile in water containing 0.1% FA) to obtain the title compound (yellow solid, 28 mg, yield: 38.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.58 (s, 1H), 8.45 (s, 1H), 8.13 (s, 1H), 6.74 (s, 1H), 4.13 - 3.68 (m, 4H), 3.55 - 3.50 (m, 2H), 3.42 - 3.36 (m, 4H), 2.48 - 2.43 (m, 2H), 2.18 (s, 6H), 1.16 (s, 3H), 1.07 - 0.99 (m, 2H), 0.99 - 0.92 (m, 2H), 0.75 - 0.68 (m, 2H), 0.50 - 0.41 (m, 2H). LC/MS (ESI) (m/z): 643 [M+H]⁺.

Example

385:

8-(4-(1-(3-(dimethylamino)propoxy)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Benzyl 1-(3-hydroxypropoxy)cyclopropane-1-carboxylate

At 0°C, potassium hydroxide (525 mg, 9.36 mmol) and 3-bromopropan-1-ol (840 mg, 6.08 mmol) were added to the solution of 1-hydroxycyclopropan-1-benzyl carboxylate (900 mg, 4.68 mmol) in dimethyl sulfoxide (9 mL). The reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-45% ethyl acetate) to obtain the title compound (colorless liquid, 900 mg, yield: 76.8%). LC/MS (ESI) (m/z): 251 [M+H]⁺.

Step 2: Benzyl 1-(3-((methylsulfonyl)oxy)propoxy)cyclopropane-1-carboxylate

At 0°C, triethylamine (910 mg, 8.99 mmol) and methylsulfonyl chloride (540 mg, 4.67 mmol) were added to the solution of 1-(3-hydroxypropoxy)cyclopropan-1-benzyl carboxylate (900 mg, 3.60 mmol) in dichloromethane (9 mL). The reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (colorless liquid, 570 mg, yield: 48.2%), which was directly used in the next step without purification. LC/MS (ESI) (m/z): 329 [M+H]⁺.

Step 3: Benzyl 1-(3-(dimethylamino)propoxy)cyclopropane-1-carboxylate

At 0°C, 2 M dimethylaminetetrahydrofuran (5 mL) solution was added to the solution of 1-(3-((methylsulfonyl)oxy)propoxy)cyclopropan-1-benzyl carboxylate (570 mg, 1.74 mmol) in tetrahydrofuran (2 mL). The reaction mixture was allowed to react under a sealed condition at 65°C for 3 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was separated by column chromatography (eluent: dichloromethane/methanol, gradient: 0-8% methanol) to obtain the title compound (colorless liquid, 217 mg, yield: 45.1%). LC/MS (ESI) (m/z): 278 [M+H]⁺.

Step 4: 1-(3-(dimethylamino)propoxy)cyclopropane-1-carboxylic acid

At room temperature, palladium hydroxide (20 mg, mass fraction: 10%) was added to the solution of 1-(3-(dimethylamido)propoxy)cyclopropan-1-benzyl carboxylate (217 mg, 0.78 mmol) in ethyl acetate (3 mL). The reaction mixture was ventilated three times under an atmosphere provided by a hydrogen-filled balloon and then stirred for 2 hours at room temperature under hydrogen atmosphere. After completion of the reaction, the reaction mixture was filtered; and the filtrate of the reaction mixture was concentrated under reduced pressure to obtain a crude title compound (colorless liquid, 140 mg, yield: 95.5%), which was directly used in the next step without purification. LC/MS (ESI) (m/z): 188 [M+H]⁺.

Step

5:

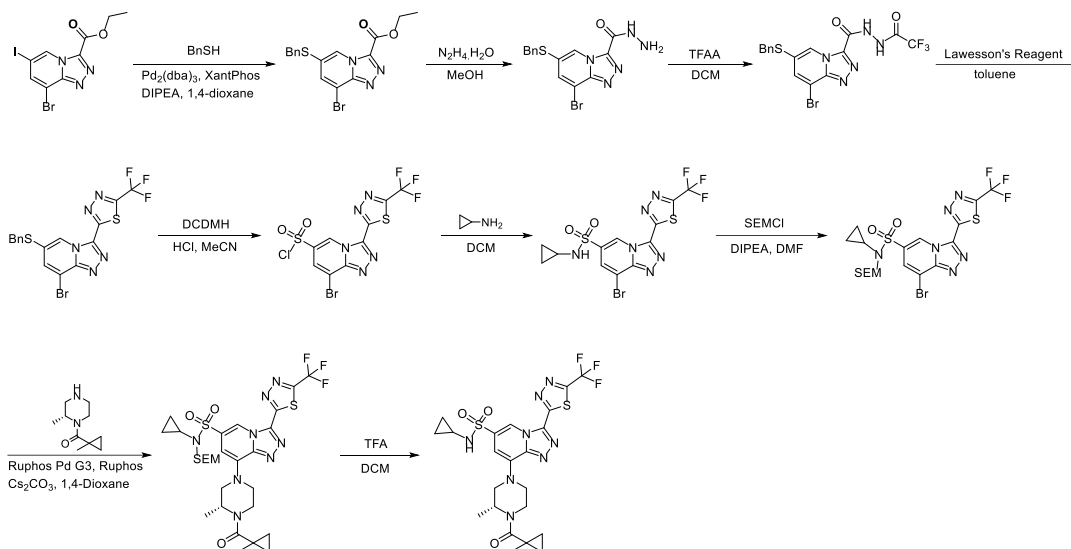
8-(4-(1-(3-(dimethylamino)propoxy)cyclopropane-1-carbonyl)piperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, 1-(3-(dimethylamino)propoxy)cyclopropan-1-carboxylic acid (32 mg, 0.17 mmol), N,N-diisopropylethylamine (55 mg, 0.43 mmol) and 2-(7-azobenzotriazol)-N,N,N',N'-tetramethylurea hexafluorophosphate (82 mg, 0.21 mmol) were added to the solution of N-(1-methylcyclopropyl)-8-(piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (70 mg, 0.14 mmol) in N,N-dimethylformamide (2 mL). The reaction mixture was stirred at room temperature for 4 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, sequentially washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by pre-HPLC (C18, 10-50% acetonitrile in water containing 0.1% FA) to obtain the title compound (yellow solid, 26 mg, yield: 27.5%). ¹H NMR (400 MHz, CD₃OD) δ 9.81 (s, 1H), 7.96 (s, 1H), 6.77 (s, 1H), 4.23 - 3.85 (m, 4H), 3.61 - 3.57 (m, 2H), 3.44 - 3.39 (m, 4H), 2.76 - 2.69 (m, 2H), 2.51 (s, 6H), 1.89 - 1.82 (m, 2H), 1.27 (s, 3H), 1.15 - 1.10 (m, 2H), 1.06 - 1.02 (m, 2H), 0.85 - 0.81 (m, 2H), 0.51 (m, 2H). LC/MS (ESI) (m/z): 657 [M+H]⁺.

Example

386:

(R)-N-cyclopropyl-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide



Step 1: Ethyl 6-(benzylthio)-8-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

Under an atmosphere of nitrogen, N,N-diisopropylethylamine (2.0 g, 15.7 mmol), XantPhos (510 g, 0.503 mmol), $\text{Pd}_2(\text{dba})_3$ (480 mg, 0.503 mmol) were sequentially added to the solution of 8-bromo-6-iodo-[1,2,4]triazolo[4,3-a]pyridin-3-ethyl carboxylate (2 g, 5.25 mmol) and phenylmethyl mercaptan (0.65 g, 5.25 mmol) in 1,4-dioxane (40 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 4 hours under an atmosphere of nitrogen. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 1.5 g, yield: 78%). LC/MS (ESI) (m/z): 392 $[\text{M}+\text{H}]^+$.

Step 2: 6-(benzylthio)-8-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carbohydrazide

Under an atmosphere of nitrogen, hydrazine hydrate (660 mg, 16.6 mmol) was added to the solution of 6-(benzylthio)-8-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-ethyl carboxylate (1.3 g, 3.3 mmol) in methanol (20 mL). The reaction mixture was stirred at 60°C for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (yellow solid, 1.5 g). LC/MS (ESI) (m/z): 378 $[\text{M}+\text{H}]^+$.

Step

3:

6-(benzylthio)-8-bromo-N'-(2,2,2-trifluoroacetyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carbohydrazide

Under an atmosphere of nitrogen, trifluoroacetic anhydride (722 mg, 3.44 mmol) was added to the solution of 6-(benzylthio)-8-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-carbohydrazide (1 g, 2.64 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

pressure. The residue was purified and separated by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow solid, 750 mg, yield: 60%). LC/MS (ESI) (m/z): 474 [M+H]⁺.

Step

4:

6-(benzylthio)-8-bromo-N'-(2,2,2-trifluoroacetyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carbohydrazide

Under an atmosphere of nitrogen, the Lawesson's reagent (704 mg, 1.74 mmol) was added to the solution of 6-(benzylthio)-8-bromo-N'-(2,2,2-trifluoroacetyl)-[1,2,4]triazolo[4,3-a]pyridine-3-carbohydrazide (750 mg, 1.58 mmol) in anhydrous toluene (7.5 mL). The reaction mixture was stirred at 110°C for 4 hours. After completion of the reaction, saturated sodium bicarbonate was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-25% ethyl acetate) to obtain the title compound (yellow solid, 700 mg, yield: 94%). LC/MS (ESI) (m/z): 472 [M+H]⁺.

Step 5: 8-bromo-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonyl chloride

At 0°C, 1N hydrochloric acid (2 mL), water (2 mL) and dichlorohydantoin (941 g, 4.77 mmol) were sequentially to the solution of 2-(6-(benzylthio)-8-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-yl)-5-(trifluoromethyl)-1,3,4-thiadiazole (750 mg, 1.59 mmol) in acetonitrile (8 mL). The reaction mixture was stirred in an ice bath for 10 minutes. After completion of the reaction, water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow solid, 1.05 g). It was directly used in the next step without purification.

Step

6:

8-bromo-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

At 0°C, 8-bromo-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonyl chloride (400 mg, 0.89 mmol) was added to the solution of cyclopropylamine (255 mg, 4.46 mmol) in anhydrous dichloromethane (4 mL). The reaction mixture was stirred at room temperature for 30 minutes. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 300 mg, yield: 72%). LC/MS (ESI) (m/z): 469 [M+H]⁺.

Step

7:

8-bromo-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylmethylsilyl)ethoxy)methyl)-[1,2,4]triazol[4,3-a]pyridin-6-sulfonamide
8-bromo-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

At 0°C, N,N-diisopropylethylamine (247 mg, 1.92 mmol) and 2-(trisilicyl)ethoxymethyl chloride (160 mg, 0.96 mmol) were sequentially added to the solution of 8-bromo-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-6-sulfonamide (300 mg, 0.64 mmol) in N,N-dimethylformamide (3 mL). The reaction mixture was stirred at room temperature for one hour. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-15% ethyl acetate) to obtain the title compound (yellow solid, 300 mg, yield: 78%). LC/MS (ESI) (m/z): 599 [M+H]⁺.

Step

8:

(R)-N-cyclopropyl-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, cesium carbonate (490 mg, 1.51 mmol), Ruphos (23 mg, 0.05 mmol), Ruphos Pd G3 (42 mg, 0.05 mmol) were sequentially added to the solution of 8-bromo-N-cyclopropyl-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylmethylsilyl)ethoxy)methyl)-[1,2,4]triazol[4,3-a]pyridin-6-sulfonamide (300 mg, 0.50 mmol) and (R)-(1-methylcyclopropyl)(2-methylpiperazin-1-yl)ketone (183 mg, 1.00 mmol) in 1,4-dioxane (6 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80 °C for 3 hours under an atmosphere of nitrogen. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 40-80% ethyl acetate) to obtain the title compound (yellow solid, 150 mg, yield: 43%). LC/MS (ESI) (m/z): 701 [M+H]⁺.

Step

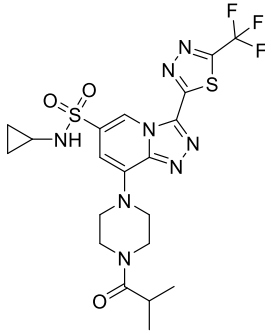
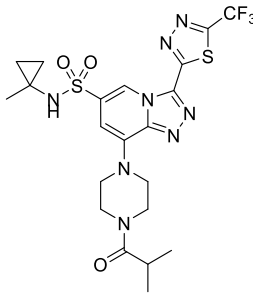
9:

(R)-N-cyclopropyl-8-(3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide

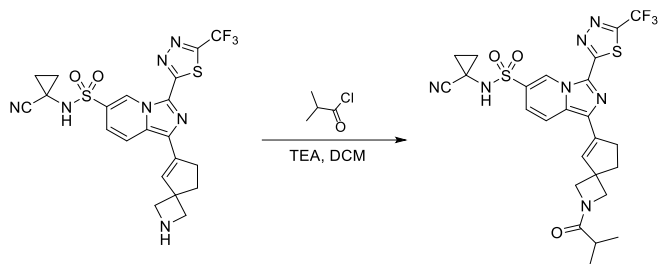
At 0°C, trifluoroacetic acid (0.5 mL) was added to the solution of (R)-N-cyclopropyl-8-(3-methyl-4-(1-methylcyclopropan-1-carbonyl)piperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazol[4,3-a]pyridin-6-sulfonamide (150 mg, 0.21 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at 0°C for one hour. After completion of the reaction, the reaction mixture was dripped to 5% aqueous sodium bicarbonate solution

cooled in the ice bath, and extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by pre-HPLC (C18, 10-50% acetonitrile in H₂O and 0.1% FA) to obtain the title compound (yellow solid, 42 mg, yield: 34%). ¹H NMR (400 MHz, DMSO) δ 9.32 (s, 1H), 8.35 (s, 1H), 6.95 (s, 1H), 4.78 – 4.66 (m, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.37 – 4.24 (m, 2H), 3.47 (s, 1H), 3.29 – 3.24 (m, 1H), 3.15 – 3.02 (m, 1H), 2.32 – 2.24 (m, 1H), 1.33 (d, *J* = 5.7 Hz, 3H), 1.29 (s, 3H), 0.93 – 0.81 (m, 2H), 0.64 – 0.48 (m, 6H). LC/MS (ESI) (*m/z*): 571 [M+H]⁺.

By referring to the preparation method in Example 386, the following examples were implemented by synthesizing a crude product according to a similar route by starting from appropriate starting materials, treating the crude product via reversed-phase HPLC, and then freeze-drying the crude product to obtain the title compound.

Example	Structure and name	Analysis data
Example 387	 N-cyclopropyl-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.59 (d, <i>J</i> = 1.0 Hz, 1H), 7.02 (s, 1H), 3.92 – 3.85 (m, 6H), 3.73 – 3.69 (m, 2H), 3.09 – 2.99 (m, 1H), 2.34 – 2.29 (m, 1H), 1.15 (d, <i>J</i> = 6.7 Hz, 6H), 0.64 – 0.58 (m, 4H). LC/MS (ESI) (<i>m/z</i>): 545 [M+H] ⁺ .
Example 388	 8-(4-isobutyrylpiperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-sulfonamide	¹ H NMR (400 MHz, CD ₃ OD) δ 9.58 (s, 1H), 7.00 (s, 1H), 3.92 – 3.88 (m, 4H), 3.87 – 3.83 (m, 2H), 3.73 – 3.69 (m, 2H), 3.09 – 3.01 (m, 1H), 1.27 (s, 3H), 1.15 (d, <i>J</i> = 6.7 Hz, 6H), 0.84 – 0.81 (m, 2H), 0.54 – 0.50 (m, 2H). LC/MS (ESI) (<i>m/z</i>): 559 [M+H] ⁺ .

Example 389:
N-(1-cyanocyclopropyl)-1-(2-isobutyryl-2-azaspiro[3.4]oct-5-en-6-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

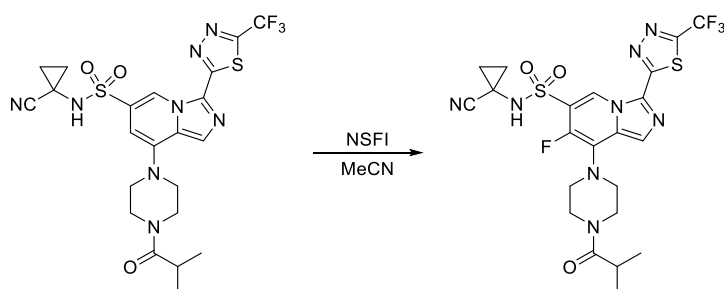
N-(1-cyanocyclopropyl)-1-(2-isobutyryl-2-azaspiro[3.4]oct-5-en-6-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, triethylamine (40 mg, 0.38 mmol) and isobutyryl chloride (25 mg, 0.24 mmol) were sequentially added to the solution of N-(1-cyanopropyl)-1-(2-azaspiro[3.4]oct-5-ene-6-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (60 mg, 0.096 mmol) in dichloromethane (4 mL); and after addition, the reaction mixture was stirred at room temperature for one hour. After completion of the reaction, water was added to the reaction mixture, which was then extracted with dichloromethane three times; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in methanol (5 mL); lithium hydroxide (10 mg, 0.19 mmol) was added at 0°C, and the reaction mixture was stirred at room temperature for 30 minutes; after completion of the reaction, the reaction mixture was added with water, and extracted with dichloromethane three times; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by pre-HPLC to obtain the title compound (yellow solid, 8.1 mg, yield: 14.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.98 (s, 1H), 9.69 (s, 1H), 8.42 (d, *J* = 9.5 Hz, 1H), 7.45 (d, *J* = 9.7 Hz, 1H), 6.73 (s, 1H), 4.30 (d, *J* = 8.3 Hz, 1H), 4.20 (d, *J* = 8.3 Hz, 1H), 3.99 (d, *J* = 9.7 Hz, 1H), 3.88 (d, *J* = 9.4 Hz, 1H), 2.99 – 2.95 (m, 2H), 2.47 – 2.44 (m, 1H), 2.36 – 2.31 (m, 2H), 1.52 – 1.49 (m, 2H), 1.39 – 1.36 (m, 2H), 1.02 – 1.00 (m, 6H). LC/MS (ESI) (*m/z*): 592 [M+H]⁺.

Example

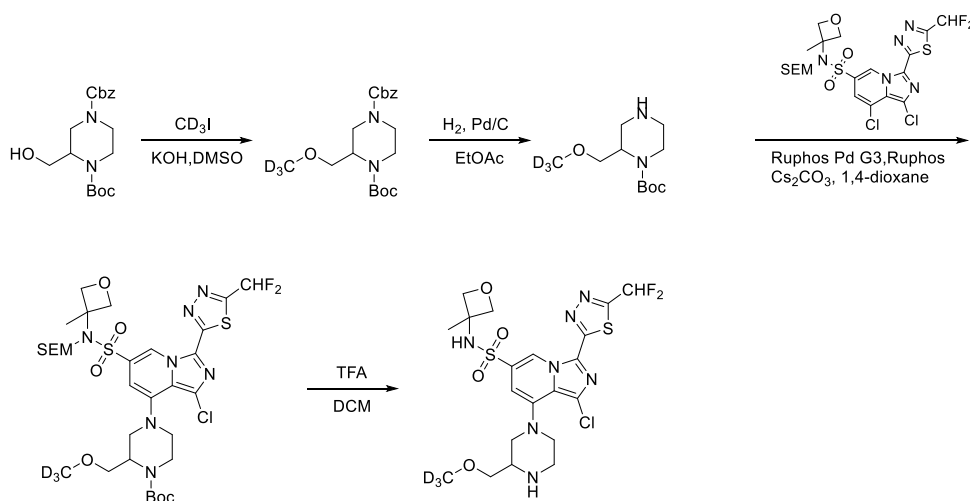
390:

N-(1-cyanocyclopropyl)-7-fluoro-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step**1:****N-(1-cyanocyclopropyl)-7-fluoro-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide**

NFSI (30 mg, 0.14 mmol) was added to the solution of N-(1-cyanocyclopropyl)-8-(4-isobutyrylpiperazin-1-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (80 mg, 0.14 mmol) in acetonitrile (2 ml). The reaction mixture was stirred at 25°C for one hour. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, and extracted with ethyl acetate three times. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 20 mg, yield: 25%). ¹H NMR (400 MHz, MeOD) δ 9.95 (d, *J* = 5.2 Hz, 1H), 7.93 (s, 1H), 3.85 – 3.80 (m, 4H), 3.50 – 3.44 (m, 4H), 3.05 – 3.00 (m, 1H), 1.59 – 1.55 (m, 2H), 1.49 – 1.45 (m, 2H), 1.15 (d, *J* = 6.7 Hz, 6H). LC/MS (ESI) (*m/z*): 586 [M+H]⁺.

Example**391:****1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-((methoxy-d3)methyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide****Step 1: 4-benzyl 1-(tert-butyl) 2-((methoxy-d3)methyl)piperazine-1,4-dicarboxylate**

At 0°C, potassium hydroxide (159 mg, 2.84 mmol) and deuterioiodomethane (613 mg, 4.26 mmol) were sequentially added to the solution of 4-benzyl-1-(tert-butyl)-2-(hydroxymethyl)piperazine-1,4-dicarboxylate (500 mg, 1.42 mmol) in DMSO (10 mL). The reaction mixture was stirred in an ice bath for 2 hours. After completion of the reaction, water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (white solid, 320 mg, yield: 30%). LC/MS (ESI) (*m/z*): 368 [M+H]⁺.

Step 2: Tert-butyl 2-((methoxy-d3)methyl)piperazine-1-carboxylate

Under an atmosphere of nitrogen, palladium on carbon (30 mg) with the mass fraction of 10% was added to the solution of 4-benzyl-1-(tert-butyl)-2-((methoxy-d3)methyl)piperazin-1,4-dicarboxylate (320 mg, 0.87 mmol) in ethyl acetate (20 mL); the flask was replaced with nitrogen gas three times and then the mixture was stirred for 2 hours under an atmosphere of hydrogen at 15psi. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (colorless oil, 180 mg, yield: 88%). LC/MS (ESI) (m/z): 234 [M+H]⁺.

Step 3: Tert-butyl 4-(1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(3-methyloxetan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-2-((methoxy-d3)methyl)piperazine-1-carboxylate

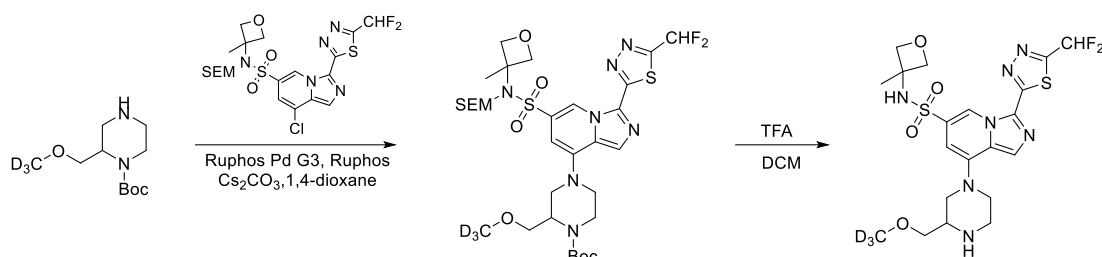
Under an atmosphere of nitrogen, cesium carbonate (97 mg, 0.30 mmol), Ruphos (9 mg, 0.02 mmol) and Ruphos Pd G₃ (9 mg, 0.01mmol) were sequentially added to the solution of 1,8-dichloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (60 mg, 0.10 mmol) and 2-((methoxy-d3)methyl)piperazin-1-tert-butyl carboxylate (30 mg, 0.13 mmol) in 1,4-dioxane (8 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 80°C for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow solid, 30 mg, yield: 37%). LC/MS (ESI) m/z: 797 [M+H]⁺.

Step 4: 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-((methoxy-d3)methyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (3 mL) was dropwise added slowly to the solution of 4-(1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(3-methyloxacyclobutan-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)aminosulfonyl)imidazo[1,5-a]pyridin-8-yl)-2-((methoxy-d₃)methyl)piperazin-1-tert-butyl carboxylate (30 mg, 0.03mmol) in dichloromethane (8 mL). The mixture was stirred at room temperature for 30 minutes. The mixture was concentrated under reduced pressure; and the residue was purified by pre-HPLC to obtain the title compound (yellow solid, 4.8 mg, yield: 22%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (d, *J* = 1.1 Hz, 1H), 9.25 (s, 1H), 7.70 (t, *J* = 53.1 Hz, 1H), 6.92 (s, 1H), 4.66 - 4.61 (m, 2H), 4.21 - 4.18 (m, 2H), 3.80 - 3.71 (m, 1H), 3.68 - 3.47 (m, 6H), 3.09 - 2.95 (m, 2H), 1.50 (s, 3H). LC/MS (ESI) (m/z): 567 [M+H]⁺.

Example**392:**

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-((methoxy-d3)methyl)piperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

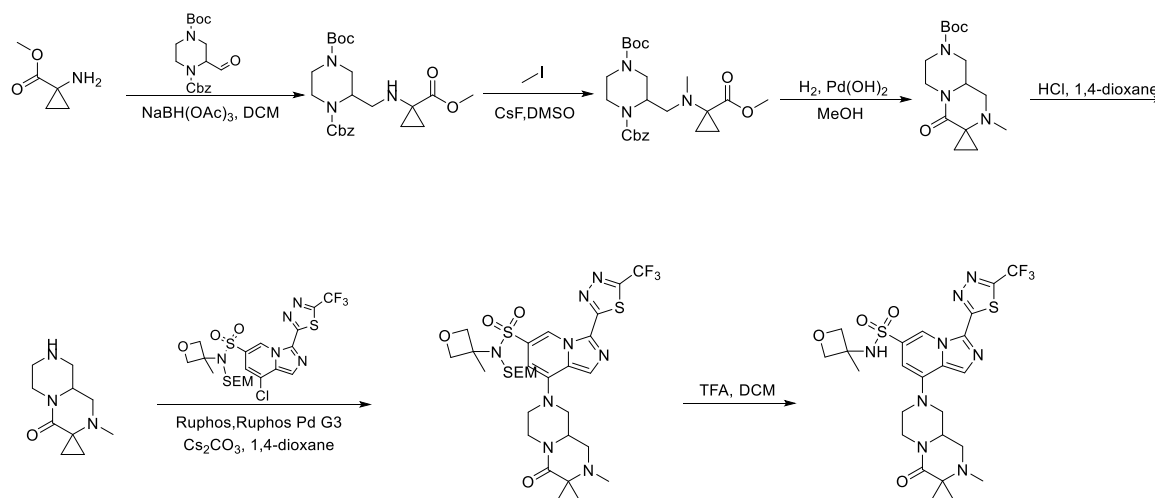


The target molecules of the title compound were obtained by referring to the preparation method in Steps 3-4 of **Example 391**. ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.63 (s, 1H), 9.22 (s, 1H), 8.87 (s, 1H), 8.14 (s, 1H), 7.69 (t, *J* = 53.1 Hz, 1H), 6.80 (s, 1H), 4.65 - 4.61 (m, 2H), 4.21 - 4.17 (m, 2H), 3.80 - 3.46 (m, 7H), 3.21 - 3.01 (m, 2H), 1.50 (s, 3H). LC/MS (ESI) (*m/z*): 533 [M+H]⁺.

Example

393:

8-(2'-methyl-4'-oxohexahydro-4'H,8'H-spiro[cyclopropane-1,3'-pyrazino[1,2-a]pyrazin]-8'-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

1-benzyl

4-(tert-butyl)

2-(((1-(methoxycarbonyl)cyclopropyl)amino)methyl)piperazine-1,4-dicarboxylate

Under an atmosphere of nitrogen, 1-aminocyclopropan-1-methyl formate (154 mg, 1.34 mmol) and sodium triacetoxyborohydride (731 mg, 3.45 mmol) were added to the solution of 4-(tert-butyl)2-formylpiperazine-1,4-dicarboxylate (400 mg, 0.89 mmol) in dichloromethane (6 mL). The reaction mixture was stirred at room temperature for 2 hours under an atmosphere of nitrogen. After completion of the reaction, saturated aqueous ammonium chloride solution was added to the reaction mixture, which was then extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by

column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow oil, 340 mg, yield: 66.0%). LC/MS (ESI) m/z: 448 [M+H]⁺.

Step 2: 1-benzyl 4-(tert-butyl) 2-(((1-(methoxycarbonyl)cyclopropyl)(methyl)amino)methyl)piperazine-1,4-dicarboxylate

At 0°C, cesium fluoride (346 mg, 2.28 mmol) and iodomethane (162 mg, 1.14 mmol) were sequentially added to the solution of 4-(tert-butyl)-2-(((1-(methoxycarbonyl)cyclopropyl)amino)methyl)piperazine-1,4-1-benzyl dicarboxylate (340 mg, 0.76 mmol) in N,N-dimethylformamide (5 mL). The reaction mixture was stirred at 80°C for 16 hours. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow oil, 140 mg, yield: 39.9%). LC/MS (ESI) (m/z): 462 [M+H]⁺.

Step 3: Tert-butyl 2'-methyl-4'-oxohexahydro-4'H,8'H-spiro[cyclopropane-1,3'-pyrazino[1,2-a]pyrazine]-8'-carboxylate

At 0°C, palladium hydroxide on carbon (28 mg) with the mass fraction of 10% was added to the solution of 4-(tert-butyl)-2-(((1-(methoxycarbonyl)cyclopropyl)(methyl)amino)methyl)piperazine-1,4-1-benzyl dicarboxylate (140 mg, 0.30 mmol) in anhydrous methanol (5 mL). The reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was filtered; and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/dichloromethane, gradient: 0-35% dichloromethane) to obtain the title compound (yellow solid, 70 mg, yield: 78.2%). LC/MS (ESI) (m/z): 296 [M+H]⁺.

Step 4: 2'-methylhexahydro-2'H,4'H-spiro[cyclopropane-1,3'-pyrazino[1,2-a]pyrazine]-4'-one

At room temperature, the solution of hydrochloric acid in 1,4-dioxane (1 mL) was added to the solution of 2'-methyl-4'-oxohexahydro-4'H,8'H-pyra[cyclopropan-1,3'-pyrazino[1,2-a]pyrazine]-8'-tert-butyl carboxylate (70 mg, 0.23 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; and the residue was added to saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow oil, 45 mg, yield: 97.2%). LC/MS (ESI) m/z: 196 [M+H]⁺.

Step 5-6: e8-(2'-methyl-4'-oxohexahydro-4'H,8'H-spiro[cyclopropane-1,3'-pyrazino[1,2-a]pyrazine]-8'-yl)-N-(3-methyloxetan-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

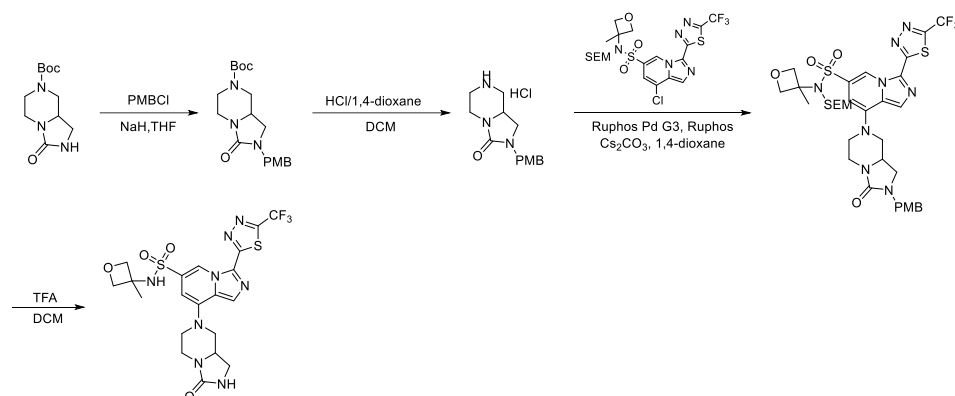
The title compound was obtained by referring to the preparation method in Steps 3-4 of **Example 391**. ¹H

NMR (400 MHz, CD₃OD) δ 9.81 (s, 1H), 7.99 (s, 1H), 6.84 - 6.79 (m, 1H), 4.80 - 4.71 (m, 4H), 4.34 - 4.30 (m, 2H), 3.87 - 3.79 (m, 2H), 3.27 - 3.24 (m, 1H), 3.18 - 3.11 (m, 2H), 3.00 - 2.93 (m, 1H), 2.83 - 2.76 (m, 1H), 2.58 (s, 3H), 1.64 (s, 3H), 1.55 - 1.50 (m, 1H), 1.32 - 1.28 (m, 1H), 1.08 - 1.02 (m, 1H), 0.96 - 0.94 (m, 1H). LC/MS (ESI) (m/z): 613 [M+H]⁺.

Example

394:

N-(3-methyloxetan-3-yl)-8-(3-oxohexahydroimidazo[1,5-a]pyrazin-7(1H)-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Tert-butyl 2-(4-methoxybenzyl)-3-oxohexahydroimidazo[1,5-a]pyrazine-7(1H)-carboxylate

At 0°C, sodium hydrogen (10 mg, 0.25 mmol) with the mass fraction of 60% and 4-methoxybenzyl chloride (45 mg, 0.3 mmol) were added to the solution of 7(1H)-(tert-butoxycarbonyl)-3-oxohexahydroimidazo[1,5-a]pyrazine (30 mg, 0.12 mmol) in tetrahydrofuran (3 mL). The reaction mixture was stirred at 65°C for 2 hours. After completion of the reaction, the reaction mixture was quenched with saturated aqueous ammonium chloride solution cooled with ice water, and extracted with ethyl acetate three times. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-50% ethyl acetate) to obtain the title compound (yellow solid, 35 mg, yield: 77.9%). LC/MS (ESI) (m/z): 362 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.25 (s, 2H), 3.94 (s, 2H), 3.79 (d, *J* = 10.8 Hz, 1H), 3.73 (s, 3H), 3.46 (dd, *J* = 11.0, 8.1 Hz, 1H), 3.20 (t, *J* = 8.7 Hz, 1H), 2.82 (t, *J* = 11.2 Hz, 1H), 2.71 (dd, *J* = 9.0, 4.7 Hz, 2H), 2.50 (s, 1H), 1.39 (s, 9H).

Step 2: 2-(4-methoxybenzyl)hexahydroimidazo[1,5-a]pyrazin-3(2H)-one hydrochloride

At 0°C, trifluoroacetic acid (0.5 mL) was added to the solution of (2-(4-methoxybenzyl)-3-oxohexahydroimidazo[1,5-a]pyrazin-7(1H)-tert-butyl carboxylate (35 mg, 0.1 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at 25°C for 1 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (yellow solid, 31 mg, yield: 99%). LC/MS (ESI) (m/z): 262 [M+H]⁺.

Step

3-4:

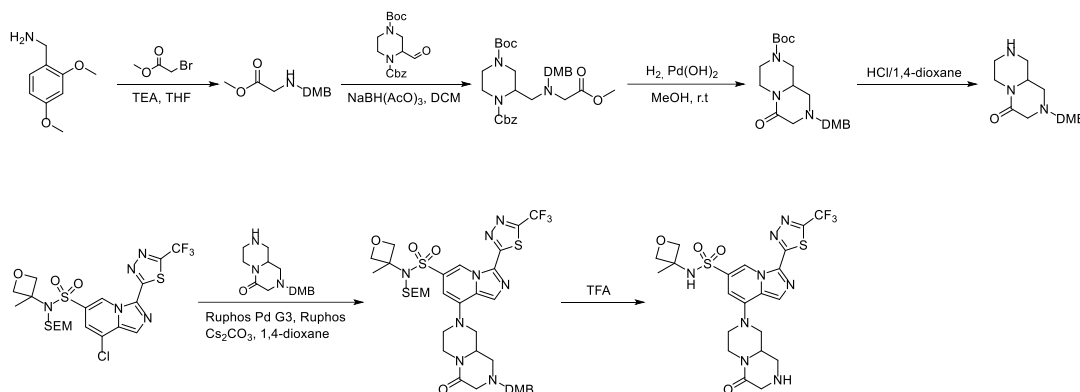
N-(3-methyloxetan-3-yl)-8-(3-oxohexahydroimidazo[1,5-a]pyrazin-7(1H)-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the preparation method in Steps 3-4 of **Example 391**. ¹H NMR (400 MHz, CD₃OD) δ 9.81 (s, 1H), 7.96 (s, 1H), 6.82 (s, 1H), 4.79 (d, *J* = 6.1 Hz, 2H), 4.34 - 4.17 (m, 2H), 4.16 - 4.09 (m, 1H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.83 - 3.77 (m, 1H), 3.71 (d, *J* = 8.2 Hz, 1H), 3.67 - 3.61 (m, 1H), 3.28 - 3.23 (m, 1H), 3.21 - 3.14 (m, 1H), 2.96 - 2.86 (m, 2H), 1.63 (s, 3H).

Example

395:

N-(3-methyloxetan-3-yl)-8-(6-oxooctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Methyl (3,4-dimethylbenzyl)glycinate

Under an atmosphere of nitrogen, triethylamine (1.81 g, 18.0 mmol) and methyl bromoacetate (1.83 g, 12.0 mmol) were added to the solution of (2,4-dimethoxyphenyl)methylamine (2 g, 12.0 mmol) in tetrahydrofuran (6 mL). The reaction mixture was stirred overnight at room temperature under an atmosphere of nitrogen. After completion of the reaction, ethyl acetate was added; the mixture was filtered; and the filtrate was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 0-100% ethyl acetate) to obtain the title compound (yellow oil, 2.3 g, yield: 80.4%). LC/MS (ESI) *m/z*: 240 [M+H]⁺.

Step

2:

1-benzyl

4-(tert-butyl)

2-(((3,4-dimethylbenzyl)(2-methoxy-2-oxoethyl)amino)methyl)piperazine-1,4-dicarboxylate

Under an atmosphere of nitrogen, (2,4-dimethoxybenzyl)glycine methyl ester (206 mg, 0.86 mmol) and sodium triacetoxyborohydride (366 mg, 1.72 mmol) were added to the solution of 4-(tert-butyl)2-formylpiperazine-1,4-dicarboxylate (200 mg, 0.57 mmol) in dichloromethane (6 mL). The reaction mixture was stirred at room temperature for 2 hours under an atmosphere of nitrogen. After completion of the reaction, saturated aqueous ammonium chloride solution was added; and the resulting mixture was extracted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography

(eluent: petroleum ether, ethyl acetate, gradient: 0-30% ethyl acetate) to obtain the title compound (yellow oil, 230 mg, yield: 70.1%). LC/MS (ESI) m/z : 572 $[M+H]^+$.

Step 3: Tert-butyl 8-(3,4-dimethylbenzyl)-6-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carboxylate

At room temperature, palladium hydroxide on carbon (40 mg) with the mass fraction of 10% was added to the solution of 4-((tert-butyl)-2-(((2,4-dimethoxybenzyl)(2-methoxy-2-oxyethyl)amino)methyl)piperazin-1,4-1-benzyl dicarboxylate (230 mg, 0.40 mmol) in methanol (6 mL). The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was filtered through diatomite; and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/dichloromethane, gradient: 0-35% dichloromethane) to obtain the title compound (yellow solid, 100 mg, yield: 61.3%). LC/MS (ESI) (m/z): 406 $[M+H]^+$.

Step 4: 2-(3,4-dimethylbenzyl)octahydro-4H-pyrazino[1,2-a]pyrazin-4-one

The solution of hydrochloric acid and 1, 4-dioxane (1 mL, 4 M) was added to the solution of 8-(2,4-dimethoxybenzyl)-6-oxooctahydro-2H-pyrazino[1,2-a]pyrazin-2-tert-butyl carboxylate (100 mg, 0.23 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, adjusted to pH 8 by adding saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow oil, 65 mg, yield: 86.3%). LC/MS (ESI) m/z : 306 $[M+H]^+$.

Step

5-6:

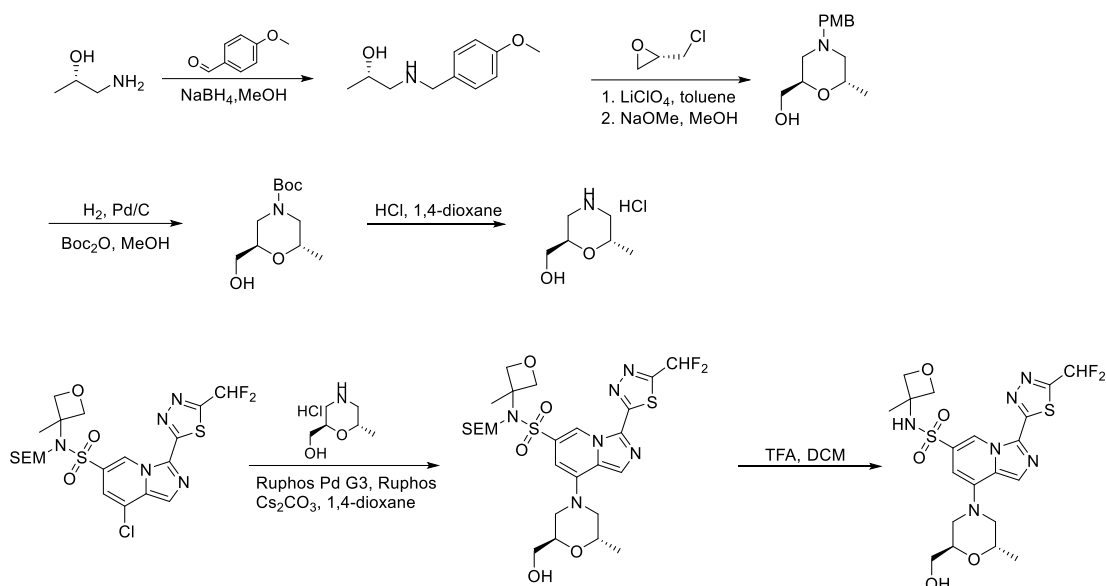
N-(3-methyloxetan-3-yl)-8-(6-oxooctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the preparation method in Steps 3-4 of **Example 391**. ^1H NMR (400 MHz, CD_3OD) δ 9.82 (s, 1H), 8.32 (s, 1H), 7.99 (s, 1H), 6.81 (s, 1H), 5.37 - 5.33 (m, 2H), 5.21 - 5.14 (m, 2H), 4.32 (d, J = 6.6 Hz, 2H), 3.64 - 3.55 (m, 3H), 2.21 - 2.17 (m, 4H), 2.04 - 2.02 (m, 2H), 1.64 (s, 3H). LC/MS (ESI) (m/z): 573 $[M+H]^+$.

Example

396:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: (S)-1-((4-methoxybenzyl)amino)propan-2-ol

Under an atmosphere of nitrogen, p-methoxybenzaldehyde (10.3 mg, 76 mmol) was added to the solution of (S)-1-aminopropan-2-ol (6 g, 80 mmol) in methanol (60 mL); the reaction mixture was stirred at room temperature for one hour under an atmosphere of nitrogen; and then, 0°C, sodium borohydride (3.0 g, 80 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 2 hours under an atmosphere of nitrogen. After completion of the reaction, saturated aqueous ammonium chloride solution was added to the reaction mixture, which was then extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (white solid, 10 g, yield: 64.1%). LC/MS (ESI) m/z : 196 $[M+H]^+$.

Step 2: ((2R,6S)-4-(4-methoxybenzyl)-6-methylmorpholin-2-yl)methanol

Under an atmosphere of nitrogen, (S)-2-(chloromethyl)ethylene oxide (3 g, 32.61 mmol) and lithium perchlorate (3.5 g, 32.6 mmol) were added to the solution of (S)-1-((4-methoxybenzyl)amino)propan-2-ol (8 g, 41.03 mmol) in toluene (60 mL). The reaction mixture was stirred at room temperature for 18 hours under an atmosphere of nitrogen. The solution of 30% sodium methoxide in methanol (25 mL) was added; after completion of the reaction, saturated aqueous ammonium chloride solution was added; and the resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-60% ethyl acetate) to obtain the title compound (yellow oil, 1.8 g, yield: 22.0%). LC/MS (ESI) m/z : 252 $[M+H]^+$.

Step 3: Tert-butyl (2R,6S)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate

At 0°C, palladium on carbon (90 mg) with the mass fraction of 10%, palladium hydroxide on carbon (90 mg) with the mass fraction of 10% and di-tert-butyl dicarbonate (1.17 g, 5.38 mmol) were added to the solution of ((2R,6S)-4-(4-methoxybenzyl)-6-methylmorpholin-2-yl) methanol (900 mg, 3.59 mmol) in anhydrous

methanol (10 mL). The flask was replaced with nitrogen gas three times and then the mixture was stirred at 60°C for 16 hours under an atmosphere of hydrogen at 15 psi. After completion of the reaction, the reaction mixture was filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/dichloromethane, gradient: 0-35% dichloromethane) to obtain the title compound (yellow oil, 690 mg, yield: 83.3%). LC/MS (ESI) (m/z): 232 [M+H]⁺.

Step 4: ((2R,6S)-6-methylmorpholin-2-yl)methanol hydrochloride

The solution of hydrogen chloride in 1,4-dioxane (3 mL) was added to the solution of (2R,6S)-2-(hydroxymethyl)-6-methylmorpholin-4-tert-butyl carboxylate (400 mg, 0.23 mmol) in 1,4-dioxane (5 mL). The reaction mixture was stirred at room temperature for 2 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain the title compound (yellow oil, 350 mg, yield: 91.3%). LC/MS (ESI) m/z: 132 [M+H]⁺.

Step

5-6:

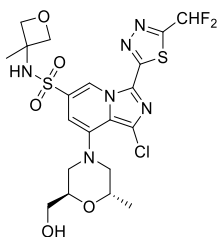
3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the preparation method in Steps 3-4 of **Example 391**. ¹H NMR (400 MHz, DMSO) δ 9.57 (s, 1H), 8.73 (s, 1H), 8.05 (s, 1H), 7.84 - 7.52 (m, 1H), 6.70 (d, *J* = 0.9 Hz, 1H), 5.01 - 4.96 (m, 1H), 4.66 - 4.61 (m, 2H), 4.20 - 4.09 (m, 3H), 3.96 - 3.83 (m, 2H), 3.67 - 3.55 (m, 2H), 3.17 - 3.13 (m, 1H), 3.01 - 2.95 (m, 1H), 1.50 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H). LC/MS (ESI) (m/z): 531 [M+H]⁺.

Example

397:

1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

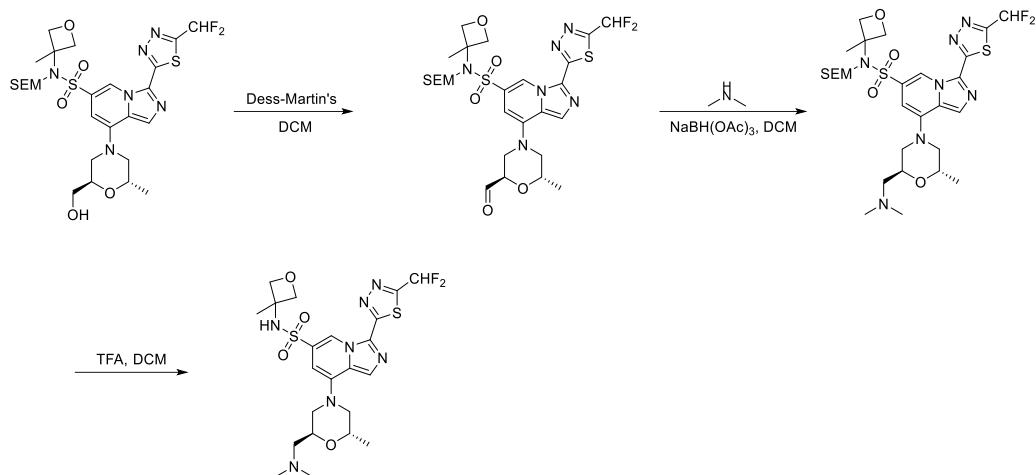


This example was implemented by referring to the synthesis method in **Example 396**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.61 (s, 1H), 8.81 (s, 1H), 7.69 (t, *J* = 53.1 Hz, 1H), 6.86 (s, 1H), 4.76 - 4.71 (m, 1H), 4.65 - 4.61 (m, 2H), 4.27 - 4.22 (m, 1H), 4.19 (d, *J* = 6.3 Hz, 2H), 4.05 - 4.00 (m, 1H), 3.67 - 3.61 (m, 2H), 3.30 - 3.26 (m, 2H), 2.93 - 2.85 (m, 1H), 2.66 - 2.60 (m, 1H), 1.50 (s, 3H), 1.23 (d, *J* = 6.3 Hz, 3H). LC/MS (ESI) (m/z): 565 [M+H]⁺.

Example

398:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6S)-2-((dimethylamino)methyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-formyl-6-methylmorpholino)-N-(3-methyloxet-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

Under an atmosphere of nitrogen, Dess-Martin periodinane (26 mg, 0.06 mmol) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxet-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (20 mg, 0.03 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 1 hours under an atmosphere of nitrogen. After completion of the reaction, the reaction mixture was diluted with dichloromethane, sequentially washed with saturated aqueous sodium sulfite solution and saturated sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (yellow oil, 19 mg, yield: 95.3%). LC/MS (ESI) m/z : 659 $[M+H]^+$.

Step

2:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6S)-2-((dimethylamino)methyl)-6-methylmorpholino)-N-(3-methyloxet-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide

At room temperature, the solution of dimethylamine in tetrahydrofuran (1 mL, 2 mol/L) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-formyl-6-methylmorpholino)-N-(3-methyloxet-3-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridine-6-sulfonamide (19 mg, 0.03 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 30 minutes under an atmosphere of nitrogen; then, sodium triacetoxyborohydride (18 mg, 0.09 mmol) was added; and the reaction mixture was continued to be stirred at room temperature for 30 minutes under an atmosphere of nitrogen. After completion of the reaction, water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the title compound (yellow oil, 19 mg, yield: 95.8%). LC/MS (ESI) (m/z):

688 [M+H]⁺.

Step

3:

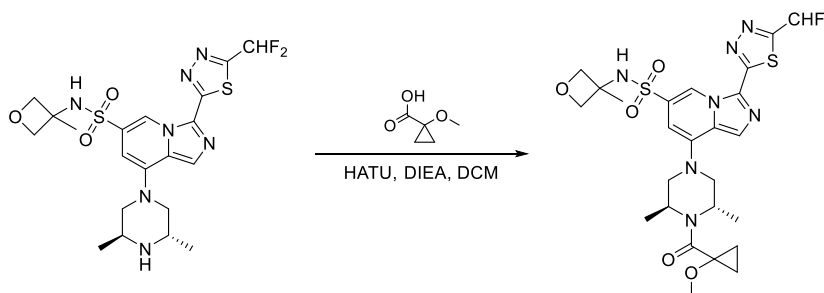
3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6S)-2-((dimethylamino)methyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, trifluoroacetic acid (1 mL) was added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6S)-2-((dimethylamino)methyl)-6-methylmorpholino)-N-(3-methyloxacyclobutan-3-yl)-N-(((2-(trimethylsilyl)ethoxy)methyl)imidazo[1,5-a]pyridin-6-sulfonamide (19 mg, 0.03 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at 25°C for 1 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by pre-HPLC to obtain the title compound (yellow solid, 5.0 mg, yield: 31.3%). ¹H NMR (400 MHz, CD₃OD) δ 9.86 (s, 1H), 7.86 (s, 1H), 7.34 (s, 1H), 6.82 - 6.77 (m, 1H), 4.81 - 4.78 (m, 2H), 4.59 - 4.54 (m, 1H), 4.40 - 4.36 (m, 1H), 4.33 - 4.31 (m, 2H), 3.85 - 3.79 (m, 1H), 3.50 - 3.43 (m, 2H), 3.37 - 3.34 (m, 1H), 3.22 - 3.15 (m, 2H), 3.00 (d, *J* = 14.3 Hz, 6H), 1.65 (s, 3H), 1.48 (d, *J* = 6.4 Hz, 3H). LC/MS (ESI) (*m/z*): 558 [M+H]⁺.

Example

399:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-4-(1-methoxycyclopropane-1-carbonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-4-(1-methoxycyclopropane-1-carbonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

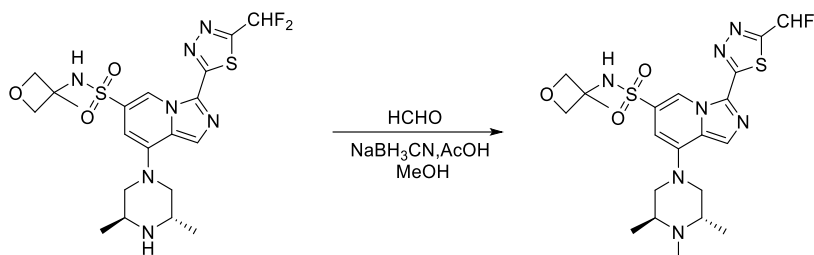
At 0°C, N,N-diisopropylethylamine (50 mg, 0.39 mmol), 1-methoxycyclopropanecarboxylic acid (19 mg, 0.17 mmol) and HATU (74 mg, 0.19 mmol) were sequentially added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxacyclobutan-3-yl)imidazo[1,5-a]pyridin-6-sulfonamide (70 mg, 0.13 mmol) in dichloromethane (2 mL); and after adding, the reaction mixture was stirred at 50°C for one hour. After completion of the reaction, water was added to the reaction mixture, which was then extracted with dichloromethane three times; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 0-70% ethyl acetate), and then

separated by pre-HPLC to obtain the title compound (yellow solid, 9.6 mg, yield: 12%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.48 (s, 1H), 8.65 (s, 1H), 8.14 (s, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.44 (s, 1H), 4.67 - 4.64 (m, 2H), 4.20 - 4.17 (m, 2H), 4.17 - 4.11 (m, 2H), 3.69 - 3.59 (m, 2H), 3.42 - 3.38 (m, 1H), 3.32 - 3.30 (m, 1H), 3.28 (s, 3H), 1.52 (s, 3H), 1.37 - 1.27 (m, 6H), 1.08 - 1.04 (m, 2H), 1.03 - 0.97 (m, 1H), 0.94 - 0.87 (m, 1H). LC/MS (ESI) (*m/z*): 612 [M+H]⁺.

Example

400:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-((3S,5S)-3,4,5-trimethylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

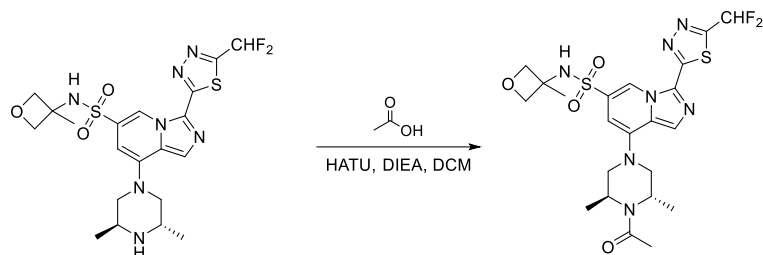
3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-((3S,5S)-3,4,5-trimethylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, formaldehyde (8 mg, 0.26 mmol), acetic acid (10 mg, 0.17 mmol) and cyano sodium borohydride (24 mg, 0.39 mmol) were sequentially added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxacyclobutan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (70 mg, 0.13 mmol) in methanol (2 mL). After adding, the reaction mixture was stirred at 0°C for 20 minutes. After completion of the reaction, water was added to the reaction mixture, which was then extracted with dichloromethane three times. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 50-80% ethyl acetate) and then purified by pre-HPLC to further obtain the title compound (yellow solid, 17 mg, yield: 24%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (d, *J* = 2.5 Hz, 1H), 8.77 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 3.1 Hz, 1H), 7.82 (t, *J* = 53.6 Hz, 1H), 6.79 (s, 1H), 4.70 - 4.61 (m, 2H), 4.25 - 4.16 (m, 2H), 3.99 - 3.92 (m, 1H), 3.86 - 3.70 (m, 4H), 3.10 - 3.02 (m, 1H), 2.89 (s, 3H), 1.55 - 1.47 (m, 6H), 1.41 (s, 3H). LC/MS (ESI) (*m/z*): 528 [M+H]⁺

Example

401:

8-((3S,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step

1:

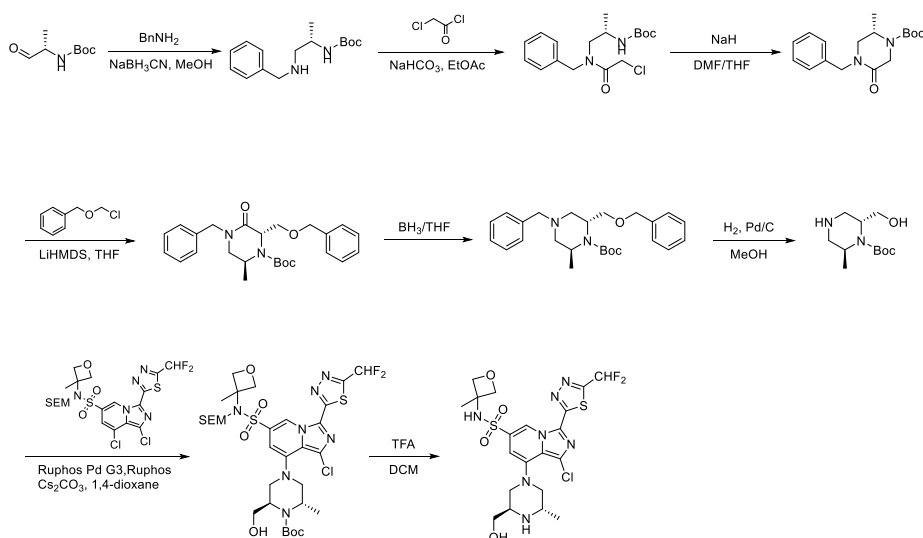
8-((3S,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetane-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

At 0°C, N,N-diisopropylethylamine (50 mg, 0.39 mmol), acetic acid (10 mg, 0.17 mmol) and HATU (74 mg, 0.19 mmol) were sequentially added to the solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetane-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (70 mg, 0.13 mmol) in dichloromethane (2 mL). After the addition, the reaction mixture was stirred at 50°C for one hour. After completion of the reaction, water was added to the reaction mixture, which was then extracted with dichloromethane three times. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by pre-HPLC to obtain the title compound (yellow solid, 14 mg, yield: 19%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.47 (s, 1H), 8.68 (s, 1H), 8.12 (s, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.38 (s, 1H), 4.68 - 4.62 (m, 2H), 4.50 - 4.41 (m, 1H), 4.34 - 4.26 (m, 1H), 4.20 - 4.12 (m, 4H), 3.69 - 3.59 (m, 2H), 2.09 (s, 3H), 1.52 (s, 3H), 1.38 - 1.31 (m, 3H), 1.23 - 1.16 (m, 3H). LC/MS (ESI) (*m/z*): 556 [M+H]⁺.

Example

402:

1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetane-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: Tert-butyl (S)-(1-(N-benzyl-2-chloroacetamido)propan-2-yl)carbamate

(S)-(1-oxoprop-2-yl)aminotert-butyl formate (5 g, 28.9 mmol) and benzylamine (3.7 g, 34.7 mmol) was dissolved in methanol (50 mL). In an ice bath, cyano sodium borohydride (5.5 g, 86.7 mmol) and acetic acid (0.327 g, 2.89 mmol) were sequentially added to the reaction mixture; and the mixture was stirred at room temperature for 16 hours. After completion of the reaction, in an ice bath for cooling, saturated ammonium chloride was added for quenching, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 10-30% ethyl acetate) to obtain the title compound (colorless oil, 5.5 g, yield: 72.4%). LC/MS (ESI) m/z: 265 [M+H]⁺.

Step 2: Tert-butyl (S)-4-benzyl-2-methyl-5-oxopiperazine-1-carboxylate

(S)-(1-(benzylamino)propan-2-yl)aminotert-butyl formate (5.5 g, 20.8 mmol) was mixed with saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL). In an ice water bath, 2-chloroacetyl chloride (4.7 g, 41.6 mmol) was added to the mixture, and stirred for 2 hours. The organic layer was separated; the aqueous phase was extracted with ethyl acetate; and the organic phase was combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 10-30% ethyl acetate) to obtain the title compound (colorless oil, 5.4 g, yield: 77.7%). LC/MS (ESI) m/z: 341 [M+H]⁺.

Step 3: Tert-butyl (2S,6S)-4-benzyl-2-((benzyloxy)methyl)-6-methyl-3-oxopiperazine-1-carboxylate

(S)-(1-(N-benzyl-2-chloroacetamido)propan-2-yl)aminotert-butyl formate (5.4 g, 15.9 mmol) was mixed with tetrahydrofuran (50 mL) and N, N-dimethylformamide (50 mL). Under cooling with ice water, sodium hydride (1.6 g, 41.3 mmol) with the mass fraction of 60% was portionwise slowly added. After adding, with the temperature rising to room temperature, the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into saturated aqueous ammonium chloride solution cooled with ice water, and then extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 10-30% ethyl acetate) to obtain the title compound (colorless oil, 2.4 g, yield: 49.7%). LC/MS (ESI) m/z: 305 [M+H]⁺.

Step 4: Tert-butyl (2S,6S)-4-benzyl-2-((benzyloxy)methyl)-6-methyl-3-oxopiperazine-1-carboxylate

(S)-4-benzyl-2-methyl-5-oxopiperazine-1-tert-butyl carboxylate (1.0 g, 3.3 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL). Under the nitrogen atmosphere, 1.0 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (4 mL, 4 mmol) was dropwise added at -78°C to the mixture. The reaction mixture was stirred at -78°C for one hour, and benzylchloromethyl ether (1.3 g, 8.6 mmol) was dropwise added. After the addition, the mixture was continued to be stirred at -78°C for one hour. At -20°C, 1N hydrochloric acid (4 mL) was added to the reaction mixture, which was then extracted with

ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 10-30% ethyl acetate) to obtain the title compound (colorless oil, 800 mg, yield: 77.7%). LC/MS (ESI) m/z : 425 $[M+H]^+$.

Step 5: Tert-butyl (2R,6S)-4-benzyl-2-((benzyloxy)methyl)-6-methylpiperazine-1-carboxylate

(2S, 6S)-4-benzyl-2-((benzyloxy)methyl)-6-methyl-3-oxopiperazin-1-tert-butyl carboxylate (800 mg, 1.9 mmol) was dissolved in tetrahydrofuran (10 mL). At 0°C, 1M borane /tetrahydrofuran solution (9.5 mL, 9.5 mmol) was dropwise added to the mixture. After the addition, the mixture was heated to 60°C, and stirred for 6 hours. Methanol (-10 mL) was added to the reaction mixture at 0°C for quenching, and the resulting mixture was stirred at 60°C for one hour. The resulting mixture was concentrated under reduced pressure; and the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 10-30% ethyl acetate) to obtain the title compound (colorless oil, 450 mg, yield: 57.8%). LC/MS (ESI) m/z : 411 $[M+H]^+$.

Step 6: Tert-butyl (2R,6S)-2-(hydroxymethyl)-6-methylpiperazine-1-carboxylate

In an autoclave, palladium hydroxide on carbon (50 mg) with the mass fraction of 20% was added to the solution of (2R,6S)-4-benzyl-2-((benzyloxy)methyl)-6-methylpiperazin-1-tert-butyl carboxylate (200 mg, 488 mmol) in methanol (5 mL); the flask was replaced with nitrogen gas three times and then the mixture was stirred for 16 hours at room temperature under an atmosphere of hydrogen at 1 MPa. After completion of the reaction, the reaction mixture was filtered through diatomite, and the filtrate was concentrated under reduced pressure to obtain the title compound (white solid, 90 mg, yield: 80.4%). LC/MS (ESI) (m/z): 231 $[M+H]^+$.

Step

7-8:

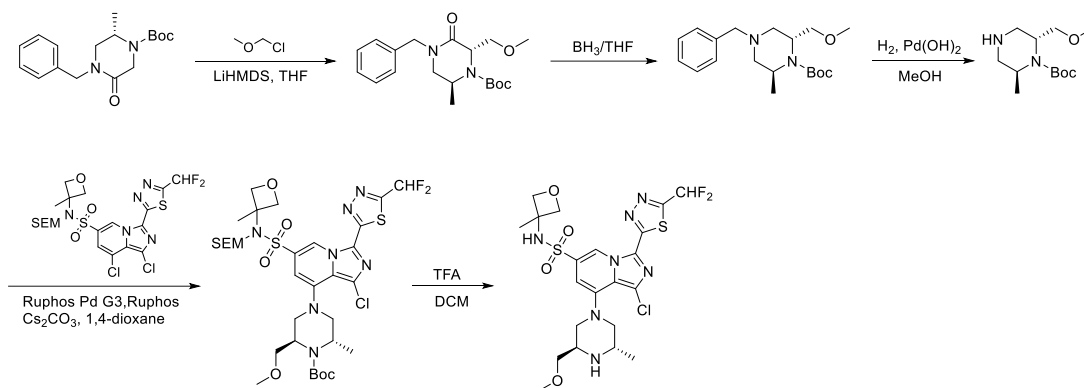
1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the preparation method in Steps 3-4 of **Example 391**. ^1H NMR (400 MHz, CD_3OD) δ 9.91 (d, J = 1.1 Hz, 1H), 7.35 (t, J = 53.5 Hz, 1H), 6.95 (d, J = 1.1 Hz, 1H), 4.40 - 4.32 (m, 2H), 4.07 - 3.86 (m, 4H), 3.74 - 3.58 (m, 2H), 3.39 - 3.32 (m, 2H), 3.26 - 3.21 (m, 1H), 3.12 - 2.96 (m, 1H), 1.66 (s, 3H), 1.53 (d, J = 4.8 Hz, 3H). LC/MS (ESI) (m/z): 564 $[M+H]^+$.

Example

403:

1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(methoxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Step 1: tert-butyl (2S,6S)-4-benzyl-2-(methoxymethyl)-6-methyl-3-oxopiperazine-1-carboxylate

At -78°C , 1.0 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (2 mL, 1.97 mmol) was dropwise added slowly to the solution of (S)-4-benzyl-2-methyl-5-oxopiperazin-1-tert-butyl carboxylate (500 mg, 1.64 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was stirred at -78°C for one hour; chloromethyl methyl ether (328 mg, 4.10 mmol) was then dropwise added; and the mixture was continued to be stirred for one hour. After completion of the reaction, 1 N hydrochloric acid (2 mL) was added at -20°C ; the reaction mixture was extracted with ethyl acetate; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether, ethyl acetate, gradient: 10-30% ethyl acetate) to obtain the title compound (colorless oil, 200 mg, yield: 34.8%). LC/MS (ESI) m/z : 349 $[\text{M}+\text{H}]^{+}$.

Step 2: Tert-butyl (2R,6S)-4-benzyl-2-(methoxymethyl)-6-methylpiperazine-1-carboxylate

At 0°C , 1.0 M borane/tetrahydrofuran solution (2.9 mL, 2.85 mmol) was added was dropwise added slowly to the solution of (2S,6S)-4-benzyl-2-(methoxymethyl)-6-methyl-3-oxopiperazin-1-tert-butyl carboxylate (200 mg, 0.57 mmol) in anhydrous tetrahydrofuran (10 mL). The reaction mixture was stirred at 60°C for 6 hours. After completion of the reaction, methanol (-5 mL) was added to the reaction mixture at 0°C for quenching, and then the mixture was heated to 60°C , and stirred for one hour. The resulting mixture was concentrated under reduced pressure; and the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, gradient: 10-30% ethyl acetate) to obtain the title compound (colorless oil, 120 mg, yield: 62.8%). LC/MS (ESI) m/z : 335 $[\text{M}+\text{H}]^{+}$.

Step 3: Tert-butyl (2R,6S)-2-(methoxymethyl)-6-methylpiperazine-1-carboxylate

At room temperature, palladium hydroxide on carbon (10 mg) with the mass fraction of 10% was added to the solution of (2R,6S)-4-benzyl-2-(methoxymethyl)-6-methylpiperazin-1-tert-butyl carboxylate (120 mg, 0.36 mmol) in methanol (2 mL). The reaction mixture was ventilated three times under an atmosphere of nitrogen and then stirred for one hour at room temperature under an atmosphere provided by a hydrogen-filled balloon. After completion of the reaction, the reaction mixture was filtered through diatomite, and the filtrate was concentrated under reduced pressure to obtain a crude title compound (colorless oil, 85 mg, yield: 96.9%), which was directly used in the next step without purification. ^1H NMR (400 MHz, CDCl_3)

δ 3.94 - 3.89 (m, 1H), 3.85 - 3.79 (m, 1H), 3.63 - 3.58 (m, 1H), 3.52 - 3.47 (m, 1H), 3.37 (s, 3H), 3.35 - 3.32 (m, 1H), 3.13 - 3.10 (m, 2H), 2.75 - 2.69 (m, 1H), 1.47 (s, 9H), 1.34 (d, J = 6.6 Hz, 3H). LC/MS (ESI) (m/z): 245 $[M+H]^+$.

Step

4-5:

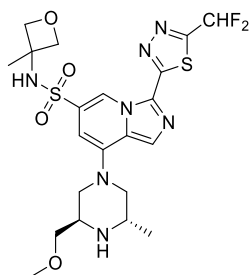
1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(methoxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

The title compound was obtained by referring to the preparation method in Steps 3-4 of **Example 391**. ^1H NMR (400 MHz, CD_3OD) δ 9.90 (d, J = 1.7 Hz, 1H), 7.34 (t, J = 53.5 Hz, 1H), 6.92 (s, 1H), 4.83 - 4.79 (m, 2H), 4.34 (d, J = 5.9 Hz, 2H), 4.04 - 3.93 (m, 2H), 3.88 - 3.82 (m, 1H), 3.75 - 3.71 (m, 1H), 3.65 - 3.59 (m, 2H), 3.46 (s, 3H), 3.21 - 3.13 (m, 2H), 1.65 (s, 3H), 1.49 (d, J = 3.7 Hz, 3H). LC/MS (ESI) (m/z): 578 $[M+H]^+$.

Example

404:

3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(methoxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



The title compound was obtained by referring to the preparation method in **Example 403**. ^1H NMR (400 MHz, CD_3OD) δ 9.82 (s, 1H), 7.88 (s, 1H), 7.33 (t, J = 53.5 Hz, 1H), 6.79 (s, 1H), 4.79 (d, J = 6.0 Hz, 2H), 4.32 (d, J = 5.2 Hz, 2H), 3.92 - 3.85 (m, 1H), 3.83 - 3.77 (m, 2H), 3.76 - 3.71 (m, 1H), 3.64 - 3.53 (m, 2H), 3.50 (s, 3H), 3.46 - 3.40 (m, 1H), 3.26 - 3.19 (m, 1H), 1.63 (s, 3H), 1.47 (d, J = 5.4 Hz, 3H). LC/MS (ESI) (m/z): 544 $[M+H]^+$.

Effect Examples

Experimental Approaches:

1. Biochemical Assay

1) 20 nL compounds at different concentrations were added to the 384-well plate (final concentrations of compounds: 1000 nM, 300 nM, 100 nM, 30 nM, 10 nM, 3 nM, 1 nM, 0.3 nM, 0.1 nM, 0.03 nM, 0 nM) by Echo 550 (LABCYTE, #550);

2) preparation of reaction buffer I: 50 mM Tris (2-amino-2-hydroxymethyl-1,3-propanediol, Sigma, #T1503) at pH 7.4, 0.015% Triton X-100 (4-(1,1,3,3-tetramethylbutyl)phenyl-polyethylene glycol, Sigma, #T8787), 0.1% BSA (bovine serum albumin, Sigma, #A1933), 5 mM KCl, and 66.2 μM TFMU-ADPr

(fluorescein-4-trifluoromethylumbelliferone-ADP ribose);

3) the reaction buffer I was added to the 384-well plate at 10 μ L/well;

4) preparation of reaction buffer II: 50 mM Tris at PH 7.4, 0.015% Triton X-100, 0.1% BSA, 5 mM KCl, and 4 nM PARG (poly ADP-ribosomal hydrolase);

5) the reaction buffer II was added to the 384-well plate at 10 μ L/well to initiate the reaction;

6) the plate was incubated at room temperature for 3min;

7) the 384-well plate was placed in the microplate reader, and shook for 5 seconds for signal detection;

8) Data analysis was carried out using GraphPad software to determine IC₅₀.

2. Cell Function Assay (In-Cell Western)

1) Human breast squamous carcinoma cells HCC1806 (ATCC) were seeded to the 384-well plate (Corning, #3764) at 20,000 cells/well, incubated for 24 h in a CO₂ (5%) incubator at 37°C to allow for complete adherence of the cells;

2) 120 nL compounds or DMSO were added to the 384-well plate by Echo 550 (LABCYTE, #550) (final concentrations of compounds: 30000 nM, 10000 nM, 3000 nM, 1000 nM, 300 nM, 100 nM, 30 nM, 10 nM, 3 nM, 1 nM, 0 nM), and then the cells were incubated for 1 h in a CO₂ (5%) incubator at 37°C;

3) 40 nL MMS (methyl mesylate, Sigma, #129925)(final concentration: 0.5mM) was added to the plate by Echo 550, and the cells were treated for 1 h in a CO₂ (5%) incubator at 37°C 4) the culture medium was discarded, and the cells were fixed with 50 μ L/well 3.7% paraformaldehyde for 20 min at room temperature;

5) the cells were washed three times with PBST (136 mM NaCl, 2.6 mM KCl, 8 mM Na₂HPO₄, 2 mM KH₂PO₄, 0.05% Tween-20) buffer, each time 5 min;

6) after fixation, the cells were permeabilized with 50 μ L/well 0.3% Triton X-100 for 5 min at room temperature;

7) the cells were washed three times with PBST (136 mM NaCl, 2.6 mM KCl, 8 mM Na₂HPO₄, 2 mM KH₂PO₄, 0.05% Tween-20) buffer, each time 5 min;

8) after cell permeabilization, the cells were blocked with 50 μ L/well 5% BSA for 90 min at room temperature ;

9) after cell blocking, the PAR/pADPr (R&D, #4335-MC-100) antibody (diluted 1:2000) was added at 25 μ L/well to the cells and then incubated for 16 h at 4°C;

10) the cells were washed four times with PBST (136 mM NaCl, 2.6 mM KCl, 8 mM Na₂HPO₄, 2 mM KH₂PO₄, 0.05% Tween-20) buffer, each time 5 min;

11) 800CW goat anti-mouse (diluted 1:200) (LiCRO, #926-32210) and DRAQ5 (diluted 1:200) (Cell Signaling Technology, #4084L) were added at 25 μ L/well to the cells, and then incubated for 60 minutes at room temperature;

12) the cells were washed four times with PBST (136 mM NaCl, 2.6 mM KCl, 8 mM Na₂HPO₄, 2 mM KH₂PO₄, 0.05% Tween-20) buffer, each time 5 min;

13) PBS (136 mM NaCl, 2.6 mM KCl, 8 mM Na₂HPO₄, 2 mM KH₂PO₄) buffer was added to the cells, and Li-Cor Bioscience scanning was used for signal detection;

14) the data were analyzed using GraphPad software to determine the IC₅₀.

3. Cell Viability Assay

1) HCC1806 (Nanjing Cobioer, ATCC cell bank, 200 cells/well) was plated in the 96-well plate, and incubated for 24 h in a CO₂ (5%) incubator at 37°C to allow for complete adherence of the cells;

2) media (100 µL/well) containing the compounds (final concentrations of compounds: 30000 nM, 10000 nM, 3000 nM, 1000 nM, 300 nM, 100 nM, 30 nM, 10 nM, 3 nM, 1 nM, 0 nM) were added to the cells, and then, incubated for 7 days in the CO₂ (5%) incubator at 37°C;

3) the culture plate containing the cells was held at room temperature for 30 min to equilibrate the plate and its contents to room temperature;

4) CellTiter-Glo (Promega: V9101) reagent (100 µL/well) was added to each well of cells, and the contents were mixed on an orbital shaker for 2 minutes;

5) the plate was incubated at room temperature for 10 min to stabilize the signal, and detected by the microplate reader (Thermo: VarioskanLUX);

6) data were analyzed using GraphPad software to determine the IC₅₀.

Data list:

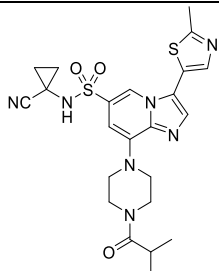
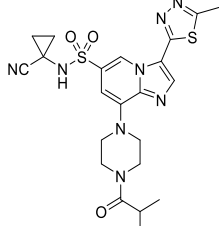
Biochemical assay and cell function assay:

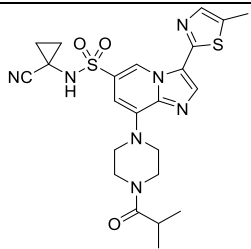
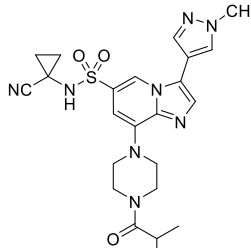
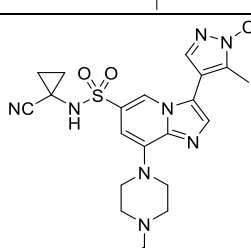
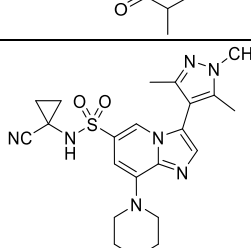
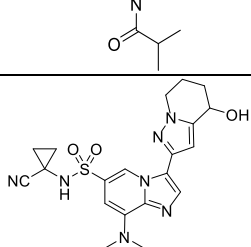
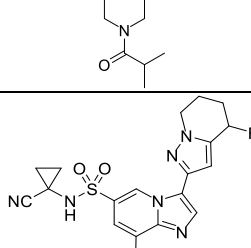
++++ ≤ 100nM, 100 nM < +++ ≤ 500 nM, 500 nM < ++ ≤ 1 µM, + > 1 µM;

Cell viability assay:

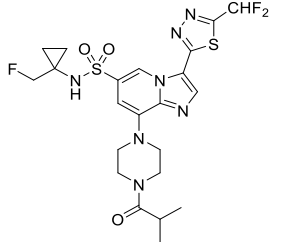
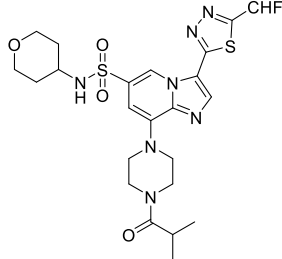
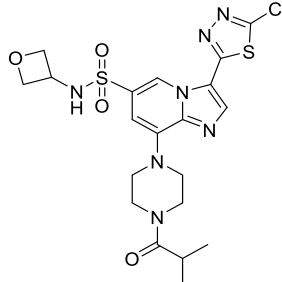
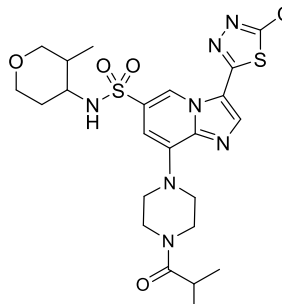
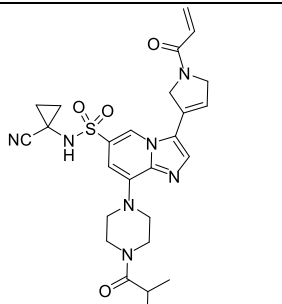
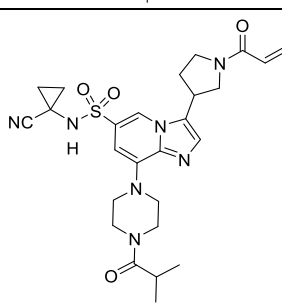
++++ ≤ 500 nM, 500 nM < +++ ≤ 5 µM, 5 µM < ++ ≤ 30 µM, + > 30 µM;

NT = not detected;

Example	Compound structure	IC ₅₀ (nM) in biochemical assay	IC ₅₀ (nM) in cell function assay	IC ₅₀ (nM) in cell viability assay
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2		NT	NT	NT

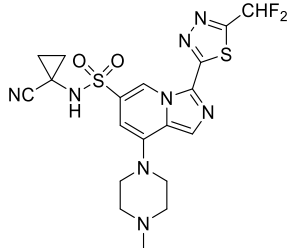
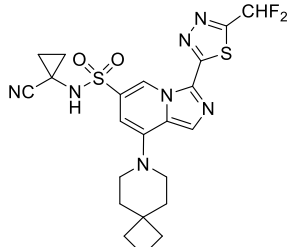
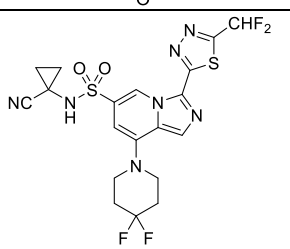
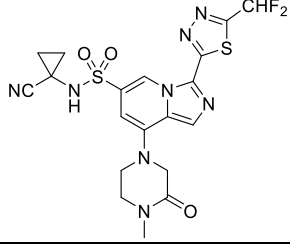
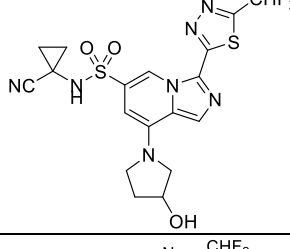
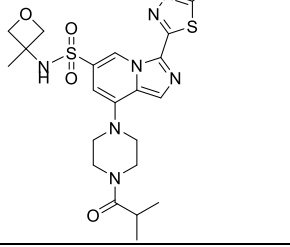
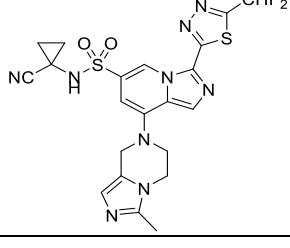
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8		NT	NT	NT

9		NT	NT	NT
10		++	NT	NT
11		++++	++++	+++
12		++++	NT	++++
13		++++	NT	NT

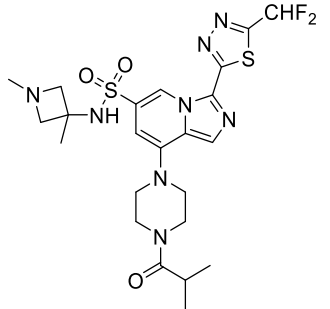
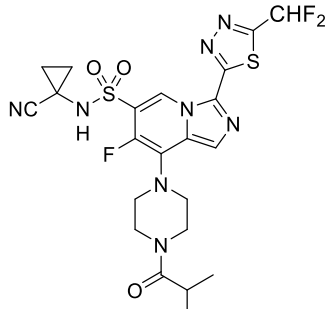
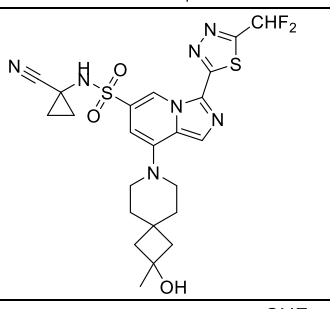
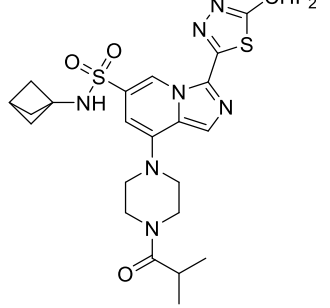
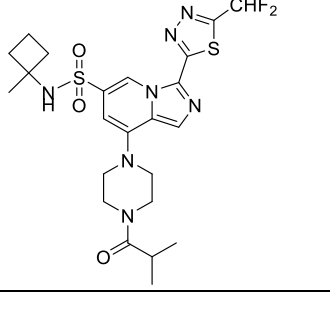
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19		NT	NT	NT

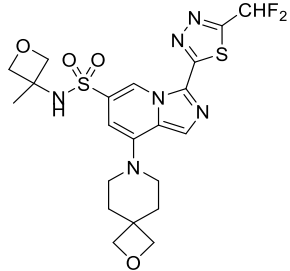
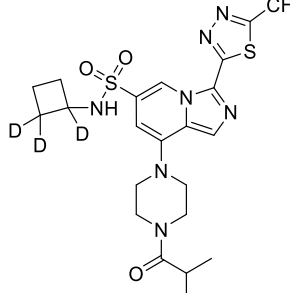
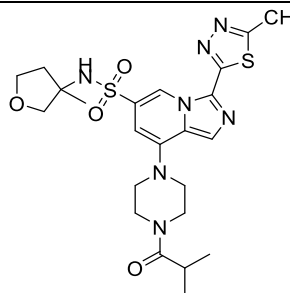
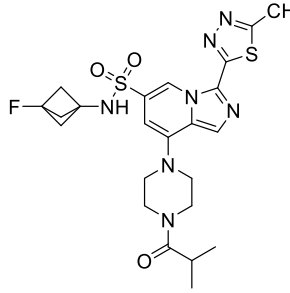
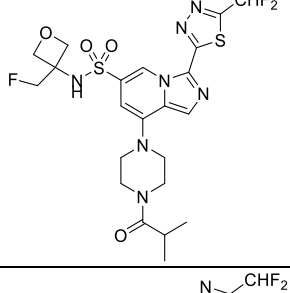
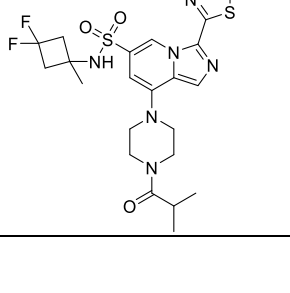
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21		NT	NT	NT
22		++++	NT	+
23		NT	NT	NT
24		++++	++++	++++
25		++++	NT	++++

32		++++	++++	+++
33		++++	+++	NT
34		++++	++++	++++
35		++	NT	NT
36		++	NT	NT
37		++++	NT	NT

38		++++	NT	NT
39		++++	++++	++++
40		++++	+++	+++
41		++++	NT	NT
42		++++	NT	NT
43		++++	++++	++++
44		++++	NT	++

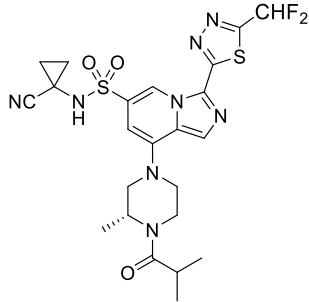
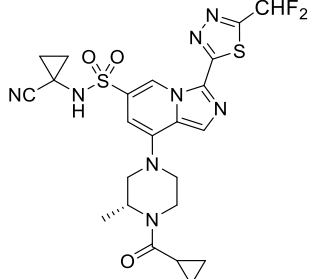
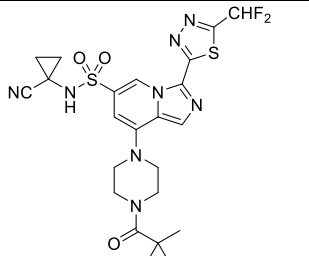
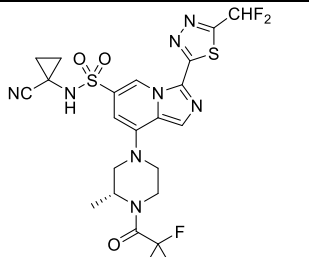
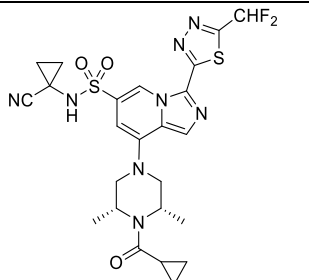
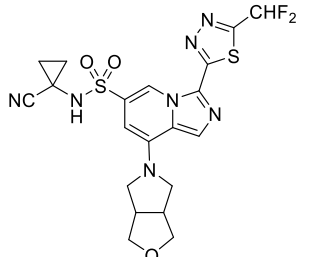
45		+++	NT	NT
46		++++	NT	NT
47		++++	NT	NT
48		++++	NT	NT
49		++++	NT	++
50		+	NT	+

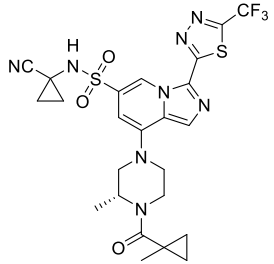
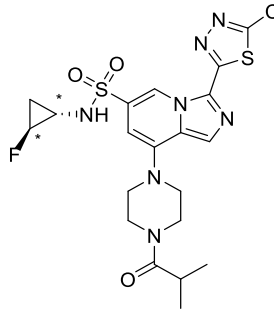
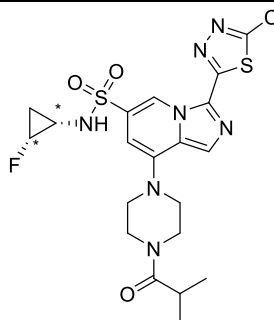
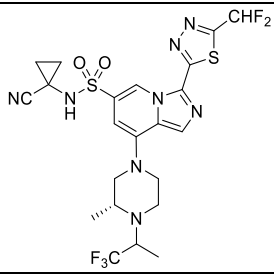
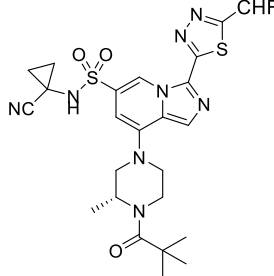
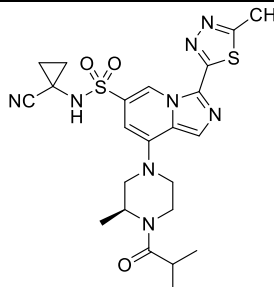
51		+	NT	+
52		++++	+++	+++
53		++++	+++	+++
54		++++	++++	++
55		++++	+++	++

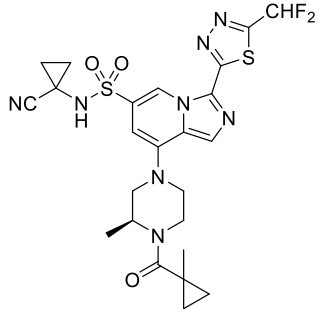
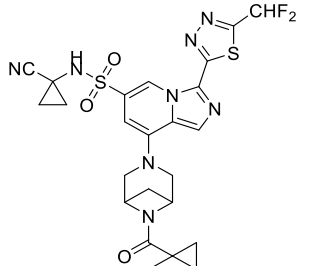
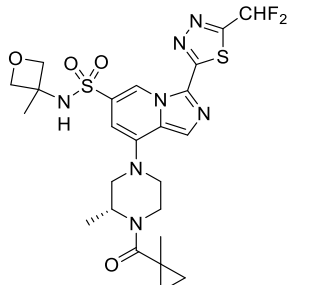
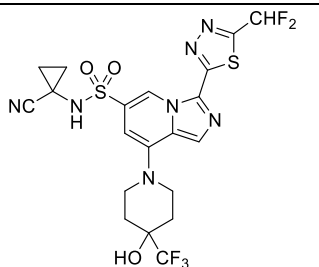
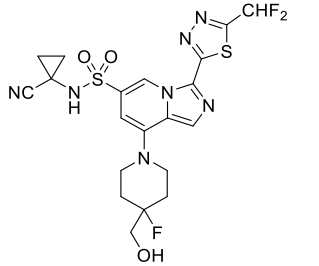
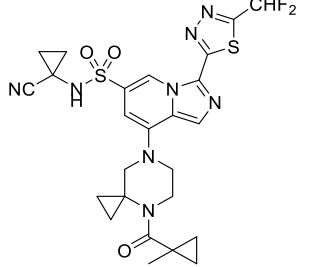
56		++++	++++	+++
57		++++	+	+
58		++++	+	+
59		+	NT	+
60		++++	++++	++++
61		+++	NT	+

62		++++	++++	++++
63		++++	++++	++++
64		++++	++++	++++
65		++++	+++	++
66		++++	++++	+++
67		++++	++++	+++

68		++++	++++	+++
69		++++	++++	++++
70		++++	NT	+++
71		++++	++++	++++
72		++++	NT	+++
73		++++	NT	+++

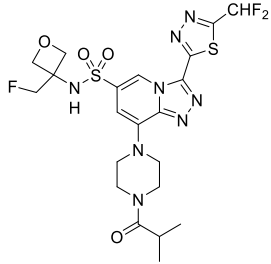
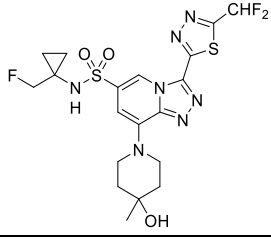
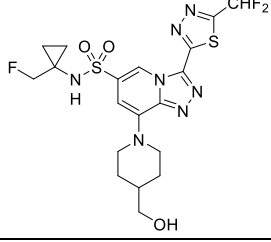
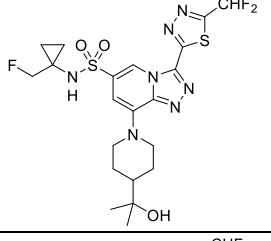
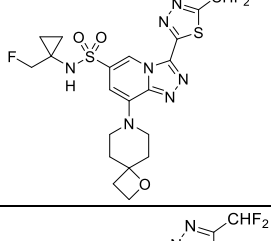
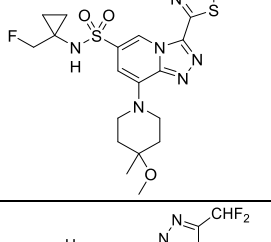
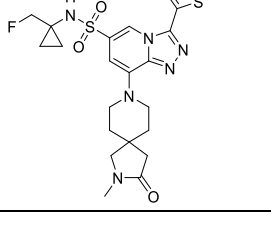
74		++++	++++	++++
75		++++	++++	++++
76		++++	++++	++++
77		++++	++++	+++
78		++++	++++	+++
79		++++	NT	+++

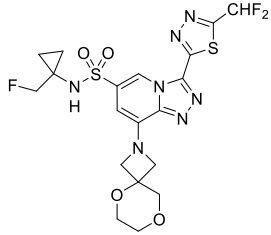
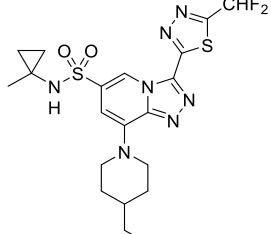
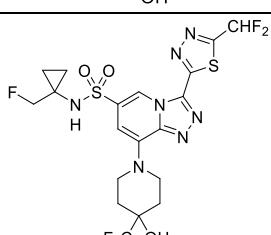
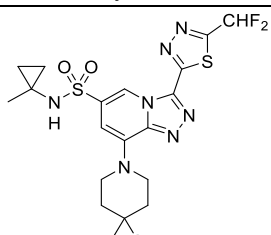
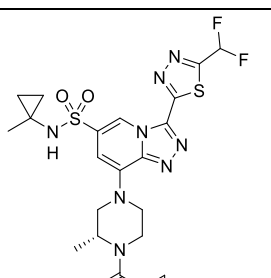
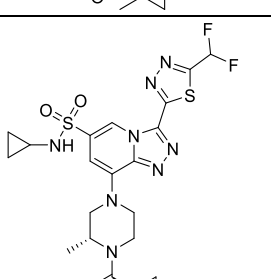
80		++++	++++	+++
81		+	NT	++
82		+++	NT	++
83		+++	NT	+++
84		++++	++++	++++
85		++++	++++	+++

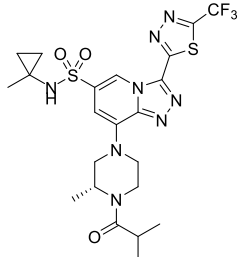
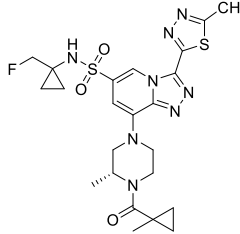
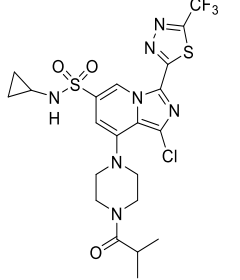
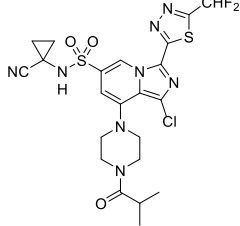
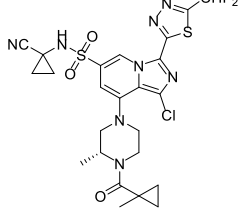
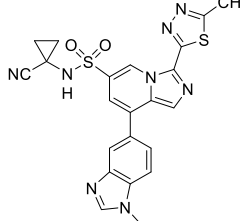
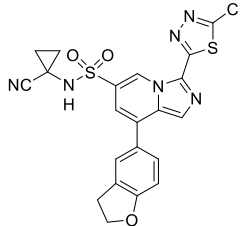
86		++++	++++	+++
87		++++	++++	+++
88		++++	++++	+++
89		+++	NT	+++
90		++++	NT	+++
91		++++	NT	++++

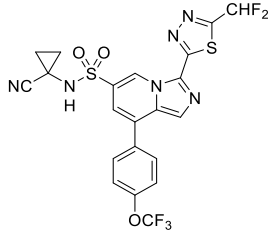
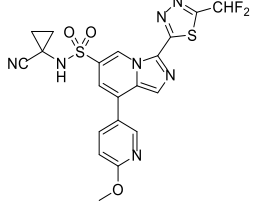
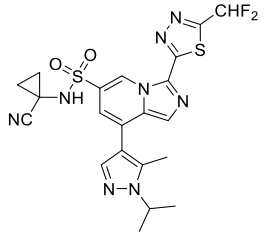
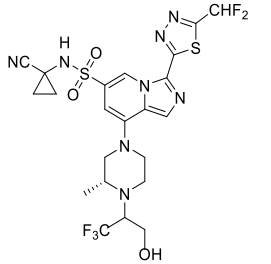
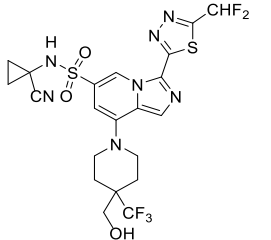
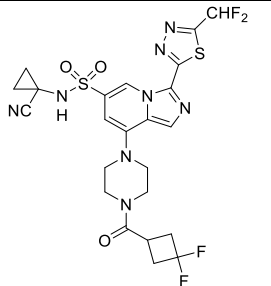
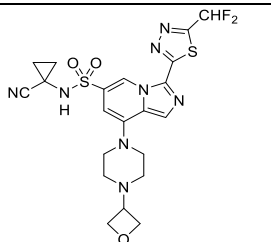
92		++++	NT	+++
93		++++	NT	+++
94		++++	++++	++++
95		++++	NT	+++
96		++++	++++	++++
97		++++	++++	++++
98		NT	NT	+

99		++++	++++	++++
100		++++	++++	++++
101		++++	+	++
102		++++	++++	++
103		++++	++++	+++
104		++++	++++	++++
105		++++	NT	++

106		++++	NT	++
107		++++	++++	+++
108		++++	++++	+++
109		++++	NT	++
110		++++	++++	+++
111		++++	++++	+++
112		++++	++++	+++

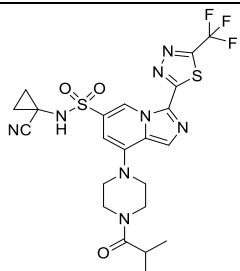
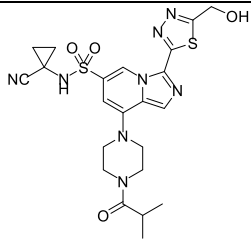
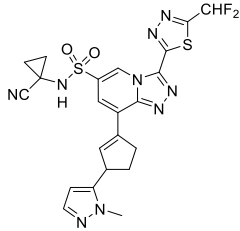
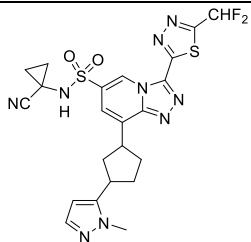
113		++++	++++	+++
114		++++	++++	+++
115		++++	++++	++++
116		++++	NT	+++
117		++++	++++	++++
118		++++	NT	+++

119		++++	NT	++++
120		++++	++++	++++
121		++++	NT	NT
122		++++	++++	++++
123		++++	++++	+++
139		++++	NT	NT
140		++++	NT	NT

141		+++	NT	NT
142		++++	NT	NT
143		++++	NT	NT
144		+++	NT	++
145		+++	NT	+++
146		++++	++++	+++
147		++++	NT	++

148		++++	+	++
149		++++	++++	+++
150		++++	NT	NT
151		+++	NT	NT
152		++++	++++	+++
153		++++	++++	+++
154		++++	++++	+++

155		++++	+++	+++
156		++++	++++	++++
159		++++	++++	++++
161		++++	++++	++++
162		++	NT	++
163		++++	++++	++++

167		++++	++++	++++
366		++++	++++	++
367		++++	NT	++
378		++++	NT	++

Example	IC ₅₀ (nM) in biochemical assay	IC ₅₀ (nM) in cell function assay	IC ₅₀ (nM) in cell viability assay
1	1535	NT	NT
2	2100	NT	NT
3	33.1	NT	NT
4	NT	NT	NT
5	NT	NT	NT
6	NT	NT	NT
7	NT	NT	NT
8	9685	NT	NT
9	NT	NT	NT
10	NT	NT	NT
11	1.99	22.4	456

12	2.4	9.15	500
13	10.9	NT	NT
14	0.76	2.01	64
15	NT	NT	NT
16	29.7	NT	NT
17	NT	NT	NT
18	40	NT	NT
19	7244	NT	NT
20	178	NT	NT
21	912	NT	NT
22	5.17	NT	30000
23	NT	NT	NT
24	2.46	52.6	500
25	4.84	NT	490
26	5.37	4693	NT
27	4.98	76.3	3526
28	33	NT	NT
29	94.6	NT	NT
30	88.9	NT	NT
31	0.84	4.7	101
32	0.77	10.8	222
33	6.52	155	NT
34	1.22	5.77	77
35	128	NT	NT
36	649	NT	NT
37	4.7	166	2666
38	16.4	NT	NT
39	2.72	13.2	220
40	8.37	309	1408
41	29.8	NT	NT
42	18	NT	NT
43	0.96	9.32	283
44	10.7	NT	14000

45	135	NT	NT
46	6.31	NT	NT
47	5.91	NT	NT
48	13.2	NT	NT
49	38.4	NT	11932
50	NT	NT	NT
51	NT	NT	NT
52	3.66	53.2	738
53	2.37	145	1376
54	11.4	26.5	9382
55	3.92	324	9890
56	0.86	22.9	802
57	21.2	1106	NT
58	25.1	2872	NT
59	NT	NT	NT
60	0.19	2.85	438
61	121	NT	NT
62	3.75	3.52	242
63	2.12	1.356	48
64	3.44	6.92	220
65	7.02	122	6000
66	2.89	18.2	1002
67	8.83	40.1	1931
68	25.1	34.7	1664
69	20.0	9.05	432
70	32.9	NT	2068
71	1.32	0.67	55
72	17.8	NT	805
73	41.7	NT	2046
74	6.61	1.50	200
75	13.2	3.78	370
76	13.8	3.59	450
77	24.0	14.8	1587

78	7.59	7.34	866
79	52.5	NT	3090
80	28.8	7.57	764
81	NT	NT	10735
82	209	NT	7049
83	347	NT	5016
84	11.0	6.85	472
85	15.2	13.7	1051
86	16.6	11.4	1331
87	7.24	49.9	2458
88	8.69	6.77	1525
89	115	NT	2436
90	34.7	NT	1526
91	31.6	NT	264
92	27.5	NT	974
93	75.9	NT	1759
94	9.55	23.4	350
95	100	NT	4514
96	2.09	1.68	100
97	5.01	7.52	135
98	NT	NT	NT
99	6.51	26.8	372
100	1.99	4.96	448
101	8.15	1543	20000
102	2.54	32.1	5000
103	1.50	33.6	1619
104	0.65	9.76	206
105	78.6	NT	10000
106	28.2	NT	5000
107	2.04	74.0	513
108	1.50	22.6	520
109	30.5	NT	7000
110	14.0	89.5	850

111	0.37	72.9	916
112	3.67	36.3	3540
113	5.20	9.00	1140
114	1.57	17.5	462
115	1.88	8.51	215
116	50	NT	2700
117	8.71	1.49	256
118	72.4	NT	1113
119	41.7	NT	431
120	1.49	2.28	218
121	60.1	NT	2588
122	3.16	4.58	218
123	9.12	7.13	584
124	2.54	NT	759
125	31.2	NT	518
126	5.34	NT	602
127	1.01	NT	95
128	0.99	NT	28
129	0.16	NT	12.7
130	36.3	NT	1200
131	22.9	NT	1685
132	60.1	NT	2588
133	13.18	NT	NT
134	69.18	NT	NT
135	12.58	NT	213
136	7.94	NT	199
137	15.84	NT	332
138	0.93	NT	NT
139	45.6	NT	NT
140	26.2	NT	NT
141	280	NT	NT
142	38.4	NT	NT
143	12	NT	NT

144	263	NT	7018
145	316	NT	1877
146	11.5	28.9	692
147	34.1	NT	9944
148	2.04	8507	8809
149	6.23	57.7	3453
150	8.29	NT	NT
151	178	NT	NT
152	13.2	2.89	990
153	5.34	2.99	352
154	8.22	9.94	2000
155	1.68	39.1	727
156	6.92	12.0	280
157	33.1	NT	1015
158	15.84	NT	1093
159	0.46	1.12	199
160	0.23	NT	23.5
161	0.88	1.02	77
162	525	NT	6069
163	1.58	5.14	87
164	3.31	NT	100
165	20.0	NT	1000
166	13.2	NT	882
167	16.6	6.34	290
168	0.15	NT	14
169	1.82	NT	27
170	1.66	NT	122
171	0.71	NT	32
172	10	NT	308
173	50.1	NT	400
174	5.01	NT	856
175	18.2	NT	565
176	4.37	NT	1340

177	0.54	NT	15
178	1.18	NT	945
179	0.35	NT	24.0
180	5.62	NT	517
181	1.78	NT	151
182	0.53	NT	128
183	0.91	NT	26.8
184	1.15	NT	18.0
185	4.58	NT	797
186	5.62	NT	485
187	3.37	NT	874
188	0.71	NT	85.0
189	3.55	NT	112
190	6.23	NT	593
191	32.0	NT	723
192	0.83	NT	30.0
193	0.36	NT	5.76
194	3.21	NT	84.8
195	5.62	NT	666
196	<0.10	NT	6.34
197	0.19	NT	6.58
198	0.66	NT	27.8
199	0.34	NT	11.5
200	0.63	NT	54.6
201	0.14	NT	9.06
202	1.16	NT	133
203	0.91	NT	26.8
204	36.3	NT	360
205	22.9	NT	699
206	21.9	NT	1178
207	39.8	NT	1200
208	110	NT	3350
209	60.3	NT	765

210	83.2	NT	929
211	209	NT	222
212	110	NT	3000
213	31.6	NT	1200
214	174	NT	4000
215	69.2	NT	1500
216	31.6	NT	2338
217	66.1	NT	3069
218	39.8	NT	1046
219	100	NT	4613
220	57.5	NT	664
221	43.7	NT	150
222	2.09	NT	1672
223	1.45	NT	250
224	13.8	NT	1024
225	7.94	NT	600
226	26.3	NT	4854
227	5.01	NT	300
228	0.38	NT	107
229	3.31	NT	800
230	120	NT	8000
231	8.32	NT	500
232	31.6	NT	953
233	45.7	NT	3000
234	13.2	NT	4000
235	4.37	NT	4937
236	3.80	NT	1100
237	2.88	NT	4393
238	38.0	NT	15000
239	380	NT	9786
240	13.2	NT	2437
241	24.0	NT	4183
242	52.5	NT	2981

243	871	NT	200
244	75.9	NT	9000
245	28.8	NT	2362
246	NT	NT	NT
247	NT	NT	27235
248	692	NT	6441
249	115	NT	7321
250	38.0	NT	1283
251	6.03	NT	8784
252	16.6	NT	2000
253	57.5	NT	1000
254	11.5	NT	700
255	17.4	NT	420
256	8.71	NT	80.0
257	191	NT	2107
258	550	NT	2832
259	45.7	NT	1500
260	28.8	NT	250
261	100	NT	370
262	NT	NT	2000
263	NT	NT	4500
264	75.9	NT	6640
265	158	NT	8000
266	132	NT	370
267	NT	NT	1500
268	100	NT	2211
269	79.4	NT	19952
270	91.2	NT	35925
271	11.5	NT	36240
272	7.24	NT	5410
273	1.91	NT	5939
274	41.7	NT	700
275	22.9	NT	472

276	45.7	NT	1750
277	25.1	NT	4474
278	40.7	NT	1983
279	95.5	NT	29853
280	45.7	NT	NT
281	66.1	NT	229
282	20.0	NT	84.3
283	3.80	NT	539
284	16.6	NT	310
285	20.0	NT	246
286	3.98	NT	235
287	4.37	NT	137
288	6.03	NT	NT
289	1.51	NT	6148
290	14.5	NT	151
291	9.55	NT	65
292	4.57	NT	40
293	9.12	NT	97
294	12.0	NT	110
295	39.8	NT	2818
296	3.02	NT	38.7
297	55.0	NT	362
298	19.1	NT	175
299	24.0	NT	1032
300	31.6	NT	403
301	50.1	NT	436
302	15.4	NT	329
303	20.9	NT	435
304	3.86	NT	70.0
305	6.91	NT	130
306	6.11	NT	89
307	4.13	NT	540
308	0.73	NT	104

309	1.03	NT	570
310	<0.10	NT	38.0
311	0.21	NT	234
312	<0.10	NT	6.02
313	1.64	NT	2050
314	0.68	NT	241
315	0.96	NT	5700
316	4.46	NT	918
317	3.54	NT	1140
318	1.84	NT	363
319	5.62	NT	147
320	2.71	NT	93.9
321	2.93	NT	175
322	16.5	NT	334
323	5.41	NT	181
324	4.29	NT	205
325	4.46	NT	120
326	4.82	NT	257
327	0.15	NT	6.13
328	1.21	NT	55.6
329	7.64	NT	187
330	6.55	NT	194
331	0.44	NT	78.1
332	10.8	NT	745
333	3.83	NT	310
334	6.31	NT	354
335	6.55	NT	480
336	54.1	NT	1078
337	4.82	NT	245
338	0.48	NT	50.0
339	3.16	NT	226
340	2.15	NT	1585
341	2.42	NT	139

342	3.04	NT	297
343	5.41	NT	852
344	38.3	NT	586
345	5.01	NT	374
346	1.53	NT	109
347	4.64	NT	282
348	1.99	NT	257
349	3.98	NT	455
350	20.0	NT	713
351	4.13	NT	163
352	15.3	NT	561
353	12.6	NT	434
354	0.27	NT	65.8
355	0.50	NT	85.0
356	6.31	NT	304.7
357	8.31	NT	208
358	15.84	NT	261
359	1.44	NT	47
360	36.31	NT	637
361	18.19	NT	642
362	6.31	NT	158
363	1.71	NT	63.0
364	41.4	NT	791
365	8.58	NT	1071
366	7.94	70.4	7728
367	32.8	NT	6777
368	13.8	NT	900
369	1.91	NT	505
370	41.7	NT	240
371	4.57	NT	360
372	3.80	NT	580
373	3.31	NT	21.1
374	NT	NT	2318

375	NT	NT	855
376	NT	NT	30000
377	1.41	NT	60.0
378	27.7	NT	6000
379	2.09	NT	20.0
380	3.31	NT	21.1
381	27.1	NT	3630
382	6.55	NT	828
383	0.25	NT	14.8
384	<0.15	NT	17.6
385	0.48	NT	40.0
386	263	NT	7881
387	38.0	NT	800
388	10.00	NT	320
389	20.0	NT	2132
390	28.2	NT	793
391	5.01	NT	177.3
392	10.96	NT	132
393	5.75	NT	222
394	6.56	NT	1700
395	NT	NT	NT
396	2.08	NT	36.8
397	13.18	NT	530
398	27.54	NT	992
399	12.6	NT	755
400	6.31	NT	267
401	158	NT	2804
402	20.89	NT	1840
403	21.87	NT	458
404	1.09	NT	27.0

4. Solubility Assay

1). Preparation of solutions:

The FaSSGF solution was prepared as follows:

a) preparation of FaSSGF buffer: dissolve 2.0 g of NaCl as the raw material in about 0.9 L of purified

water;

- b) adjustment of the pH of the buffer: adjust the pH of the buffer to 1.6 with 1N HCL, and replenish the buffer with purified water to the volume of 1L; and
- c) preparation of FaSSGF solution by addition of FaSSGF powder: add 0.06g of the FaSSGF powder to about 0.5 L of the buffer, stir until the powder was completely dissolved, and make up for the volume (1L) with the buffer.

The FaSSIF solution was prepared as follows:

- a) preparation of FaSSIF buffer: dissolve 0.42 g of NaOH, 3.44 g of anhydrous NaH_2PO_4 , and 6.19 g of NaCl as raw materials in about 0.9 L of purified water;
- b) adjustment the pH of the buffer: adjust the pH of the buffer to 6.5 with 1 N NaOH or 1 N HCL, and replenish the buffer with purified water to the volume of 1 L; and
- c) preparation of FaSSIF solution by addition of FaSSIF powder: add 2.24g of the FaSSIF powder to about 0.5 L of the buffer, stir until the powder was completely dissolved, and make up for the volume (1L) with the buffer.

2). Preparation of the solution of control compound:

The control compound was weighed and dissolved in DMSO to 10 mM to obtain a stock solution.

3) Preparation of the solution of compound to be tested:

The compound to be tested was formulated into a 10 mM DMSO stock solution.

4) Preparation of internal standard solution:

- a) The internal standard was weighed and dissolved in DMSO to 10 mM to obtain an internal standard stock solution (ISTD stock solution).
- b) The internal standard stock solution was diluted to 500 nM (Tolbutamide) with an ACN:methano mixture (volume ratio: 1:1) to obtain a quenching solution.

5) Testing

- a) The FaSSGF solution at pH 1.6 and the FaSSIF solution at pH 6.5 were pre-warmed; and then, the compound was injected into the buffer.
- b) 8 μL of the stock solution (10 mM) of the compound to be tested/control compound was pipetted to 792 μL of the FaSSGF solution at pH 1.6, to achieve the concentration of 100 μM (as test sample for FaSSGF solubility assay).
- c) 8 μL of the stock solution (10 mM) of the compound to be tested SY002-410-01/control compound was pipetted to 792 μL of the FaSSIF solution at pH 6.5 to achieve the concentration of 100 μM (as test sample for FaSSIF solubility assay).
- d) Then, the samples for the solubility assay were transferred to a shaker and shaken for 2 h at 25°C and 1000 rpm. Once done, the samples were centrifuged at 12,000 rpm for 10 min, and the supernatant was transferred to a new tube. The supernatant was diluted 10-fold and 100-fold with the FaSSGF solution at pH

1.6 or the FaSSIF solution at pH 6.5. 20 µL of each sample (1x, 10x, 100x and standard curve) was added to 500 µL of the IS solution. The resulting mixture was vortexed vigorously for 1 min and centrifuged at 4,500 rpm for 15 min at 4°C. 150 µL of the supernatant was transferred for LC-MS/MS sample analysis.

Information of control compound:

Compound name	Manufacturer	Lot number
Ketoconazole	Sigma	SCCC4160
Propranolol	Sigma	BCCB3791

Information of reagent:

Reagent name	Manufacturer	Lot number	Storage conditions
FaSSIF, FeSSIF & FaSSGF powder	biorelevant	FFF-0722-A	2-8°C
Acetonitrile	Thermo Fisher Scientific	A998-4	RT
Methanol	Thermo Fisher Scientific	FCM#A452-4	RT

Experimental results:

Example	FaSSGF solubility (µM)	FaSSIF solubility (µM)
32	0.90	3.18
167	57.5	96.5
159	5.19	17.4
60	3.83	10.0
107	15.9	24.2
120	81.8	140
124	38.5	88.2
175	21.5	97.2
227	73.8	82.4
236	75.7	82.6
251	80.6	78.1
298	>100	97.7

5. PXR Assay

1) Information of cell line

DPX2 (HepG2 cells stably transfected with PXR and luciferase reporters) cells were purchased from Puracyp Inc (Carlsbad, CA).

2) Experimental procedures

a) Reagents and consumables

Item	Supplier	Catalog or model number
384-well plate	Corning	354660
Growth medium	Puracyp	C-500-100
Treatment medium	Puracyp	D-500-100
Fetal bovine serum	Acantor	76294-180
CellTiter-Fluor™ Cell Viability Assay Kit	Promega	G6081
One-Glo Fluorescence Detection Kit	Promega	E6120
Centrifuge	Eppendorf	5810R
Carbon dioxide incubator	Thermo Scientific	371
Cell counter	Invitrogen	Countess II
Microplate reader	Tecan	Infinite M200
TECAN	Tecan	30020020
Echo	Beckman	Echo, 655T
Shake mixer	IKA	MS 3

b) Cell seeding

The DPX2 cells were cultured in the growth medium containing 10% fetal bovine serum. The DPX2 cells in a T-75 flask were cultured in the 5% CO₂ incubator at 37°C with 95% relative humidity, and digested when the cells grew to cover 80-90% of the bottom of the flask. The surface layer of the T-75 cultured cells was washed with 10 mL of PBS; PBS was pipetted; 3-5 mL of trypsin was added; the cells were digested at 37°C for 5 minutes or until the cells were digested to be suspended; and excessive medium containing fetal bovine serum was added to stop trypsinization. The cell suspension was transferred to a conical-bottomed centrifuge tube and centrifuged at 150 g rpm for 5 minutes at room temperature; the supernatant was carefully pipetted; and the cells were resuspended with the treatment medium, with the concentration adjusted to 3.2×10⁵ cells/mL (incubation time: 24 hours, plate seeding density: 4.0×10⁵ cells/mL). 25 µL of the cell suspension was added to each well of the 384-well cell culture plate. The cell culture plate was placed and cultured for 24 h in the 5% CO₂ incubator with 95% humidity at 37°C.

c) Formulation of compound

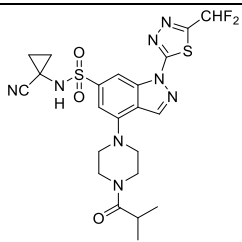
The stock solution of each of 1000× test compound, the positive control (rifampicin), and the negative control (propranolol) was prepared with DMSO. The final concentrations of the positive control (rifampicin) were 1 µM and 10 µM, and the final concentration of the negative control (propranolol) was 10 µM. The final concentrations of the test compound were 10 µM, 1 µM, 0.1 µM, or EC₅₀ (30 µM, 10 µM, 3 µM, 1 µM,

0.3 μ M, 0.1 μ M). The final concentration of DMSO was 0.1%. The cell culture plate was taken out from the incubator, and 25 nL of the stock solution of the positive control, negative control or test compound was directly added with Echo, each with three parallel concentrations. The cell culture plate was placed in the incubator and continued to be incubated for 24 h. Before starting the assay with the substrate, the cell morphology and the monolayer integrity were checked to ensure that the monolayer was of acceptable research quality.

d) Quantitative detection with PXR activation

After 24 hours of dosing, the culture could be quantitatively detected with PXR activation. The CellTiter-Fluor™ Cell Viability Assay Kit and One-Glo Luciferase reagent were equilibrated to room temperature. The GF-AFC substrate (10 μ L) was added to the assay buffer (10 ml) to develop a 2X reagent, which was then diluted into a 1X reagent with 10 ml of PBS. The ONE-Glo Luciferase substrate was added to the ONE-Glo Luciferase assay buffer. The culture plate was taken out from the incubator; the medium was discarded; 1X of CellTiter-Fluor™ reagent was poured into the loading slot; 25 μ L of reagent were added per well to the culture plate with a pipetting workstation; and the culture plate was then incubated in the incubator for 30 minutes. The cell culture plate was taken out from the incubator, and cooled slightly to room temperature; and the fluorescence value was determined with a fully automatic quantitative microplate reader, with the excitation light of 400 nm and the emission light of 505 nm. The ONE-Glo reagent was poured into the loading slot, with 25 μ L per well, and the resulting mixture was gently mixed in the plate, and incubated at room temperature for 5 minutes to determine the luminescence value.

Experimental results:

Example	PXR Activation @30uM (Fold)	PXR Activation @30uM (% Ctrl)
	6.4	44
32	2.7	19
167	5.0	34
236	1.5	7
251	1.5	11
254	1.6	12
193	2.4	15
284	1.1	7

285	1.7	10
287	1.6	15
311	1.1	5
324	1.8	14
330	1.3	9
336	0.3	2
179	3.2	22
190	2.2	12

6. Mouse PK Assay

The goal of this assay was to study the pharmacokinetics of the test compound on CD1 mice (6-8 weeks old, Zhejiang Vegavit Bio-technology Co.,Ltd.) after oral administration. The specific experimental procedures were as follows:

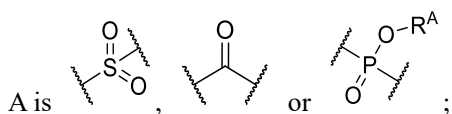
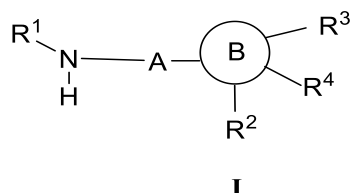
- 1) the compound was dissolved in 8% DMSO + 72% PEG 400 + 20% (10%TPGS in purified water) to arrive at the concentration of 0.5 mg/mL, and then administered orally (5 mL/Kg); and
- 2) blood samples were collected, with 0.03 mL collected at 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h, and EDTA-K2 was added. CD1 mice: Approximately 0.03 mL of blood was collected at each time point. The blood was centrifuged for 5 min at 4000 g in a centrifuge at 4°C to collect plasma. Plasma samples were aliquoted into clean polyethylene microcentrifuge tubes and then stored in a freezer at -75 ± 15°C before analysis; and
- 3) samples were analyzed, and the concentration of the compound in each plasma sample was analyzed with LC-MS/MS. For plasma measurements, pharmacokinetic parameters were calculated using WinNonlin (Phoenix™, version 8.3) or other similar software.

Experimental results:

Example	32	167
Administration dose (mg/kg)	30	30
Half-life period (hr)	1.31	2.75
Mean residence time (hr)	1.92	4.81
Time to peak (hr)	0.333	1.67
Peak concentration (ng/mL)	5317	4087
Area under the curve (0-last; hr*ng/mL)	13174	29273
Bioavailability (%)	47	85

CLAIMS

1. A compound of formula I, a pharmaceutically acceptable salt thereof or an isotopic compound thereof, wherein



R^A is hydrogen or C₁-C₆ alkyl;

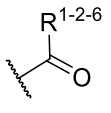
ring B is a 5-membered-fused 6-membered heteroaromatic ring unsubstituted or substituted by one or two R^B or a 5-membered-fused 5-membered heteroaromatic ring unsubstituted or substituted by one or two R^B; the heteroatom in said 5-membered-fused 6-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-membered-fused 5-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^B is each independently selected from oxo, hydroxyl, halogen or C₁-C₆ alkyl, or two R^B, together with the atoms to which they are attached, form a 3-6 membered cycloalkyl;

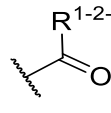
R¹ is hydroxyl, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻², 3-6 membered heterocycloalkyl unsubstituted or substituted by one or

more R¹⁻³,  or amino unsubstituted or substituted by one or two R¹⁻⁵; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻¹⁻¹, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹⁻² or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻¹⁻³; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R¹⁻¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻² is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻³ is each independently selected from deuterium, hydroxyl, cyano or halogen;

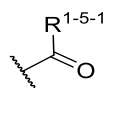
R¹⁻² is each independently selected from deuterium, hydroxyl, cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻²⁻¹, C₂-C₆ alkynyl unsubstituted or substituted by one or more R¹⁻²⁻², C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻³, C₂-C₆ alkenyl unsubstituted or substituted by one

or more R^{1-2-4} , amino unsubstituted or substituted by one or two R^{1-2-5} or ; R^{1-2-1} is each independently selected from deuterium, halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-1-1}$; $R^{1-2-1-1}$ is each independently halogen; R^{1-2-2} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-2-1}$; $R^{1-2-2-1}$ is each independently halogen; R^{1-2-3} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-3-1}$; $R^{1-2-3-1}$ is each independently halogen; R^{1-2-4} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-4-1}$; $R^{1-2-4-1}$ is each independently halogen; R^{1-2-6} is each independently amino; R^{1-2-5} is each

independently ; $R^{1-2-5-1}$ is each independently C_1 - C_6 alkyl;

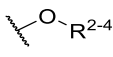
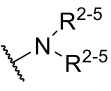
R^{1-3} is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-3-2} or C_2 - C_6 alkynyl; R^{1-3-1} is each independently halogen; R^{1-3-2} is each independently halogen;

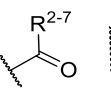
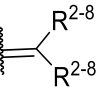
R^{1-4} is C_1 - C_6 alkyl;

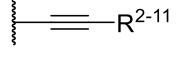
R^{1-5} is each independently selected from C_1 - C_6 alkyl,  or C_3 - C_6 cycloalkyl; R^{1-5-1} is C_1 - C_6 alkyl or amino;

or, a 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 is formed when the atom in R^1 is attached to the atom in A; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from C_1 - C_6 alkyl or oxo;

R^2 is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-2} , 4-12 membered heterocycloalkyl unsubstituted

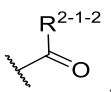
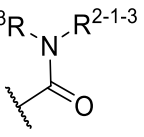
or substituted by one or more R^{2-3} , , , C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{2-6} , , , C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{2-9} , C_3 - C_6

cycloalkenyl unsubstituted or substituted by one or more R^{2-10} , or ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and

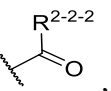
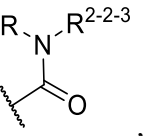
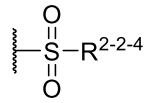
the number of heteroatom(s) is 1, 2 or 3;

R²⁻¹ is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or

more R²⁻¹⁻¹, , , or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻¹⁻⁴;

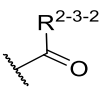
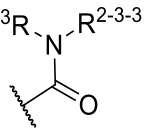
R²⁻¹⁻¹ is each independently selected from cyano or halogen; R²⁻¹⁻² is hydrogen or C₁-C₆ alkyl; R²⁻¹⁻³ is each independently selected from hydrogen or C₁-C₆ alkyl; R²⁻¹⁻⁴ is each independently selected from halogen;

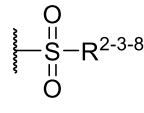
R²⁻² is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or

more R²⁻²⁻¹, , , C₁-C₆ alkoxy or  ;

R²⁻²⁻¹ is each independently selected from cyano or halogen; R²⁻²⁻² is hydrogen or C₁-C₆ alkyl; R²⁻²⁻³ is each independently selected from hydrogen or C₁-C₆ alkyl; R²⁻²⁻⁴ is each independently selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

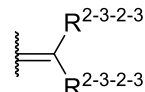
R²⁻³ is each independently selected from cyano, oxo, hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or

substituted by one or more R²⁻³⁻¹, , , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³⁻⁴, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻⁵, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻⁶, amino unsubstituted or substituted

by one or more R²⁻³⁻⁷, , or 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻³⁻⁹; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³⁻¹ is each independently selected from hydroxyl, cyano, halogen, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻¹⁻², or amino unsubstituted or substituted by one or more R²⁻³⁻¹⁻³;

R²⁻³⁻² is hydrogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻¹, C₃-C₆ cycloalkyl

unsubstituted or substituted by one or more R²⁻³⁻²⁻², , C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻⁴, 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻⁵,

or 5-10 membered heteroaryl unsubstituted or substituted by one or more $R^{2-3-2-6}$; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-3} is each independently selected from hydrogen, or C_1-C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-3-1}$;

R^{2-3-4} is each independently selected from C_1-C_6 alkyl or oxo;

R^{2-3-5} is each independently selected from halogen or deuterium;

R^{2-3-6} is each independently C_1-C_6 alkyl;

R^{2-3-7} is each independently C_1-C_6 alkyl;

R^{2-3-8} is each independently selected from C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

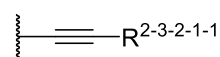
R^{2-3-9} is each independently C_1-C_6 alkyl;

$R^{2-3-1-1}$ is each independently halogen;

$R^{2-3-1-2}$ is each independently C_1-C_6 alkoxy;

$R^{2-3-1-3}$ is each independently C_1-C_6 alkyl;

$R^{2-3-2-1}$ is each independently selected from halogen, carboxyl, hydroxyl, oxo, C_1-C_6 alkoxy,



, amino unsubstituted or substituted by one or more $R^{2-3-2-1-2}$, or 5-10 membered heteroaryl unsubstituted or substituted by one or more $R^{2-3-2-1-3}$; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

$R^{2-3-2-1-1}$ is each independently selected from C_1-C_6 alkyl or 6-10 membered aryl;

$R^{2-3-2-1-2}$ is each independently C_1-C_6 alkyl;

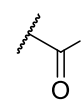
$R^{2-3-2-1-3}$ is each independently C_1-C_6 alkyl;

$R^{2-3-2-2}$ is each independently selected from halogen, hydroxyl, C_1-C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-2-1}$, C_1-C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$, or amino unsubstituted or substituted by one or more $R^{2-3-2-2-3}$;

$R^{2-3-2-2-1}$ is each independently selected from halogen or hydroxyl;

$R^{2-3-2-2-2}$ is each independently selected from carboxyl, halogen, deuterium, oxo or hydroxyl;

$R^{2-3-2-2-3}$ is each independently C_1-C_6 alkyl;

$R^{2-3-2-3}$ is each independently selected from hydrogen or  $R^{2-3-2-3-1}$; $R^{2-3-2-3-1}$ is each independently

6-10 membered aryl unsubstituted or substituted by one or more $R^{2-3-2-3-1-1}$; $R^{2-3-2-3-1-1}$ is each independently C_1-C_6 alkoxy;

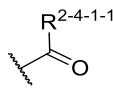
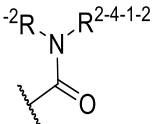
$R^{2-3-2-4}$ is each independently halogen;

$R^{2-3-2-5}$ is each independently selected from halogen, hydroxyl, oxo, C_1 - C_6 alkoxy, or C_1 - C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-5-1}$; $R^{2-3-2-5-1}$ is each independently halogen;

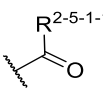
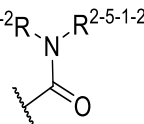
$R^{2-3-2-6}$ is each independently C_1 - C_6 alkyl;

$R^{2-3-3-1}$ is each independently amino unsubstituted or substituted by one or more $R^{2-3-3-1-1}$; $R^{2-3-3-1-1}$ is each independently C_1 - C_6 alkyl;

each R^{2-4} is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} or C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{2-4-4} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-4-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl,  or ; R^{2-4-2} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-4} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; $R^{2-4-1-1}$ is C_1 - C_6 alkyl; $R^{2-4-1-2}$ is C_1 - C_6 alkyl;

R^{2-5} is each independently selected from hydrogen, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-5-1} , , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-5-3} , or C_1 - C_6 alkyl; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-5-1} is each independently selected from  or ;

$R^{2-5-1-1}$ is hydrogen or C_1 - C_6 alkyl;

$R^{2-5-1-2}$ is each independently selected from hydrogen or C_1 - C_6 alkyl;

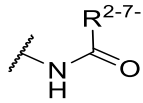
R^{2-5-2} is independently C_1 - C_6 alkyl;

R^{2-5-3} is each independently C_1 - C_6 alkoxy;

R^{2-6} is each independently selected from halogen, C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1-C_6 alkyl or ; $R^{2-6-1-1}$ is C_1-C_6 alkyl;
 R^{2-6-2} is each independently selected from halogen or C_1-C_6 alkyl;

R^{2-7} is C_1-C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-7-1} is each independently selected from halogen, C_1-C_6 alkyl,  or ; $R^{2-7-1-1}$ is C_1-C_6 alkyl; $R^{2-7-1-2}$ is C_1-C_6 alkyl;

R^{2-7-2} is each independently selected from halogen or C_1-C_6 alkyl;

R^{2-8} is each independently C_1-C_6 alkyl, or two R^{2-8} , together with the atoms to which they are attached, form a 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-8-1} is each independently ; $R^{2-8-1-1}$ is hydrogen or C_1-C_6 alkyl;

R^{2-9} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-9-1} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-9-1} is each independently C_1-C_6 alkyl;

R^{2-10} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-10-1} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-10-1} is each independently C_1-C_6 alkyl;

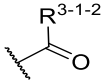
R^{2-11} is each independently selected from 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-11-1} , or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-11-2} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-11-1} is each independently C_1-C_6 alkyl; R^{2-11-2} is each independently C_1-C_6 alkyl;

R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in said 5-10 membered

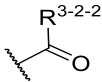
heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{3-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-1-1} or  ;

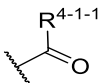
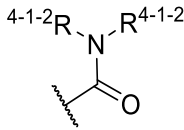
R^{3-1-1} is each independently selected from halogen or hydroxyl; R^{3-1-2} is C_1 - C_6 alkyl or C_2 - C_6 alkenyl;

R^{3-2} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-2-1} or  ;

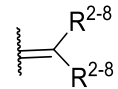
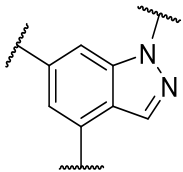
R^{3-2-1} is each independently halogen; R^{3-2-2} is C_1 - C_6 alkyl or C_2 - C_4 alkenyl;

R^4 is hydrogen, deuterium, halogen, cyano, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{4-2} ; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

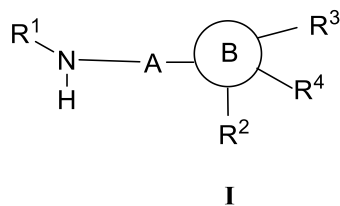
R^{4-1} is each independently selected from  or  ;

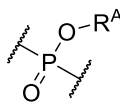
R^{4-2} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{4-2-1} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{4-1-1} is C_1 - C_6 alkyl; R^{4-1-2} is each independently C_1 - C_6 alkyl; R^{4-2-1} is each independently C_1 - C_6 alkyl; and

R^2 is  or  when ring B is  .

2. The compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to claim 1; wherein,



A is  ,  or  ;

R^A is hydrogen or C₁-C₆ alkyl;

ring B is a 5-membered-fused 6-membered heteroaromatic ring unsubstituted or substituted by one or two R^B or a 5-membered-fused 5-membered heteroaromatic ring unsubstituted or substituted by one or two R^B; the heteroatom in said 5-membered-fused 6-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-membered-fused 5-membered heteroaromatic ring is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^B is each independently selected from oxo, hydroxyl, halogen or C₁-C₆ alkyl, or two R^B, together with the atoms to which they are attached, form a 3-6 membered cycloalkyl;

R¹ is hydroxyl, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻², 3-6 membered heterocycloalkyl unsubstituted or substituted by one or

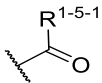
more R¹⁻³,  or amino unsubstituted or substituted by one or two R¹⁻⁵; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻¹⁻¹, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹⁻² or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻¹⁻³; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R¹⁻¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻² is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻³ is each independently selected from deuterium, hydroxyl, cyano or halogen;

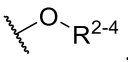
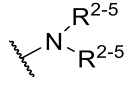
R¹⁻² is each independently selected from deuterium, hydroxyl, cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻²⁻¹, C₂-C₆ alkynyl unsubstituted or substituted by one or more R¹⁻²⁻², C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻³, C₂-C₆ alkenyl unsubstituted or substituted by one or more R¹⁻²⁻⁴ or amino unsubstituted or substituted by one or two R¹⁻²⁻⁵; R¹⁻²⁻¹ is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻¹⁻¹; R¹⁻²⁻¹⁻¹ is each independently selected from halogen; R¹⁻²⁻² is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻²⁻¹; R¹⁻²⁻²⁻¹ is each independently selected from halogen; R¹⁻²⁻³ is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻³⁻¹; R¹⁻²⁻³⁻¹ is each independently selected from halogen; R¹⁻²⁻⁴ is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻⁴⁻¹; R¹⁻²⁻⁴⁻¹ is each independently halogen;

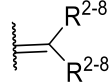
R¹⁻³ is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹ or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻³⁻²; R¹⁻³⁻¹ is each independently halogen; R¹⁻³⁻² is each independently halogen;

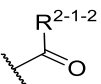
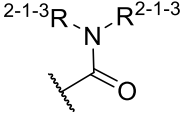
R¹⁻⁴ is C₁-C₆ alkyl;

R¹⁻⁵ is each independently selected from C₁-C₆ alkyl,  or C₃-C₆ cycloalkyl;
R¹⁻⁵⁻¹ is C₁-C₆ alkyl or amino;

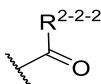
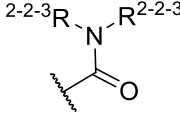
or, a 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁰ is formed when the atom in R¹ is attached to the atom in A; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R⁰ is each independently selected from C₁-C₆ alkyl or oxo;

R² is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R²⁻¹, 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻², 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³, , , C₁-C₆ alkyl unsubstituted or substituted by one

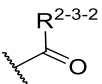
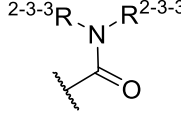
or more R²⁻⁶,  or ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻¹ is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻¹⁻¹, ,  or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻¹⁻⁴;

R²⁻¹⁻¹ is each independently selected from cyano or halogen; R²⁻¹⁻² is hydrogen or C₁-C₆ alkyl; R²⁻¹⁻³ is each independently selected from hydrogen or C₁-C₆ alkyl; R²⁻¹⁻⁴ is each independently selected from halogen;

R²⁻² is each independently selected from cyano, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻²⁻¹,  or ;

R²⁻²⁻¹ is each independently selected from cyano or halogen; R²⁻²⁻² is hydrogen or C₁-C₆ alkyl; R²⁻²⁻³ is each independently selected from hydrogen or C₁-C₆ alkyl;

R²⁻³ is each independently selected from cyano, oxo, hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻¹, , , 3-6 membered heterocycloalkyl

unsubstituted or substituted by one or more R^{2-3-4} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{2-3-5} ; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-1} is each independently selected from cyano, halogen, or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-1-1}$;

R^{2-3-2} is hydrogen or C_1 - C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-1}$;

R^{2-3-3} is each independently selected from hydrogen or C_1 - C_6 alkyl;

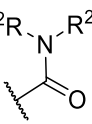
R^{2-3-4} is each independently C_1 - C_6 alkyl;

R^{2-3-5} is each independently halogen;

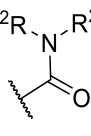
$R^{2-3-1-1}$ is each independently halogen;

$R^{2-3-2-1}$ is each independently halogen;

each R^{2-4} is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} or C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{2-4-4} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-4-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl,  or  ; R^{2-4-2} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; R^{2-4-4} is each independently selected from hydroxyl, halogen or C_1 - C_6 alkyl; $R^{2-4-1-1}$ is C_1 - C_6 alkyl; $R^{2-4-1-2}$ is C_1 - C_6 alkyl;

R^{2-5} is each independently hydrogen, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-5-1} , or  ; the heteroatom in said 4-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-5-1} is each independently selected from  or  ;

$R^{2-5-1-1}$ is hydrogen or C_1 - C_6 alkyl;

$R^{2-5-1-2}$ is each independently selected from hydrogen or C_1 - C_6 alkyl;

R^{2-5-2} is independently C_1 - C_6 alkyl;

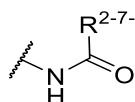
R^{2-5-2} is independently C_1 - C_6 alkyl;

R^{2-6} is each independently selected from halogen, C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl

unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1 - C_6 alkyl or ; $R^{2-6-1-1}$ is C_1 - C_6 alkyl;
 R^{2-6-2} is each independently selected from halogen or C_1 - C_6 alkyl;

R^{2-7} is C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-7-1} is each independently selected from halogen, C_1 - C_6 alkyl,  or ; $R^{2-7-1-1}$ is C_1 - C_6 alkyl; $R^{2-7-1-2}$ is C_1 - C_6 alkyl;

R^{2-7-2} is each independently selected from halogen or C_1 - C_6 alkyl;

R^{2-8} is each independently C_1 - C_6 alkyl, or two R^{2-8} , together with the atoms to which they are attached, form a 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-8-1} is each independently ; $R^{2-8-1-1}$ is hydrogen or C_1 - C_6 alkyl;

R^3 is a 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{3-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-1-1} or ;

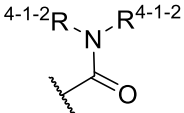
R^{3-1-1} is each independently halogen; R^{3-1-2} is C_1 - C_6 alkyl or C_2 - C_6 alkenyl;

R^{3-2} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-2-1} or ;

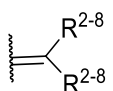
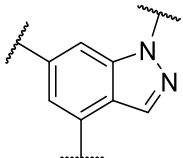
R^{3-2-1} is each independently halogen; R^{3-2-2} is C_1 - C_6 alkyl or C_2 - C_4 alkenyl;

R^4 is hydrogen, halogen, a 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{4-2} ; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{4-1} is each independently selected from  or  ;

R^{4-2} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{4-2-1} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

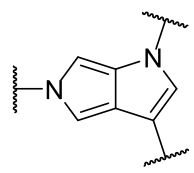
R^{4-1-1} is C_1 - C_6 alkyl; R^{4-1-2} is each independently C_1 - C_6 alkyl; R^{4-2-1} is each independently C_1 - C_6 alkyl; and

R^2 is  or  when ring B is .

3. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 2, wherein the compound of formula I satisfies one or more of the following conditions:

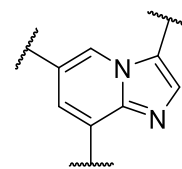
- (1) in R^A , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (2) in ring B, the heteroatom in said 5-membered-fused 5-membered heteroaromatic ring is N, and the

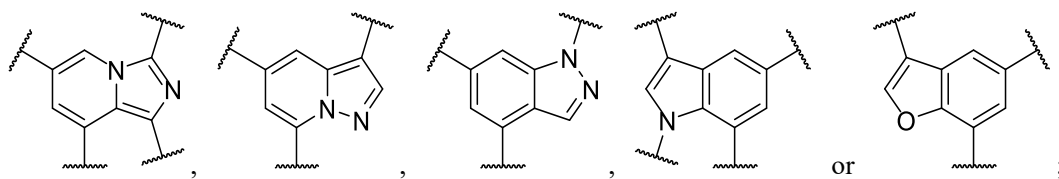
number of heteroatom(s) can be 1, 2 or 3, for example,



- (3) in ring B, said 3-6 membered cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl;
- (4) in ring B, the heteroatom in said 5-membered-fused 6-membered heteroaromatic ring is selected from N

and/or O, and the number of heteroatom(s) can be 1, 2 or 3, for example,

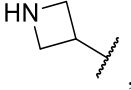


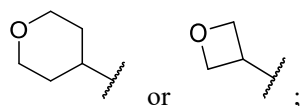


(5) in R^1 , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl;

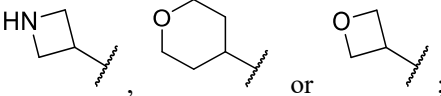
(6) in R^1 , said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclopentane, for example, cyclopropyl, cyclobutane or bicyclopentane;

(7) in R^1 , the heteroatom in said 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2; the heteroatom in said 3-6 membered heterocycloalkyl can be O or N, and the

number of heteroatom can also be 1; for example, said 3-6 membered heterocycloalkyl can be ,



(8) in R^{1-1} , the heteroatom in said 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2; the heteroatom in said 3-6 membered heterocycloalkyl can also be O or N, and the

number of heteroatom can also be 1, for example, ;

(9) in each R^{1-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(10) in each R^{1-1} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl;

(11) in each R^{1-1} , said C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;

(12) in each R^{1-1} , said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

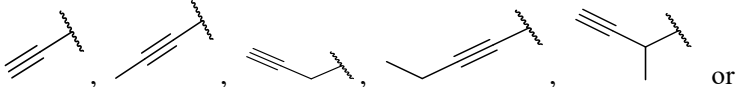
(13) in each R^{1-1-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

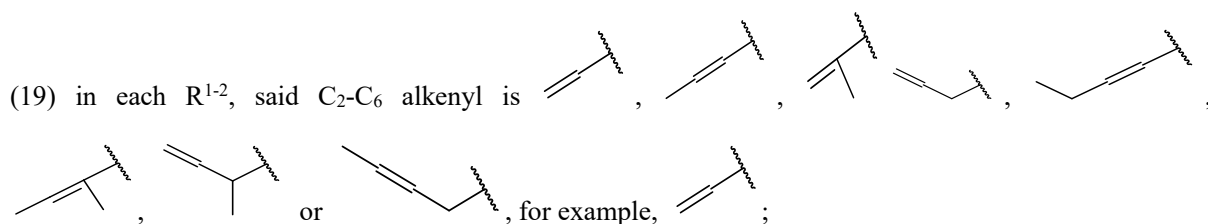
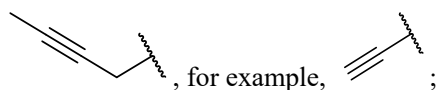
(14) in each R^{1-1-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(15) in each R^{1-1-3} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(16) in each R^{1-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(17) in each R^{1-2} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl;

(18) in each R^{1-2} , said C_2 - C_6 alkynyl is  or



(20) in R^{1-2} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;

(21) in each R^{1-2-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(22) in each R^{1-2-1} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;

(23) in each $R^{1-2-1-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(24) in each R^{1-2-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(25) in each R^{1-2-2} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;

(26) in each $R^{1-2-2-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(27) in each R^{1-2-3} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(28) in each R^{1-2-3} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;

(29) in each $R^{1-2-3-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(30) in each R^{1-2-4} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(31) in each R^{1-2-4} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;

(32) in each $R^{1-2-4-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(33) in each R^{1-2-5} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl;

(34) in each R^{1-2-5} , said C_3-C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclopentane, for example, cyclopropyl, cyclobutane or bicyclopentane;

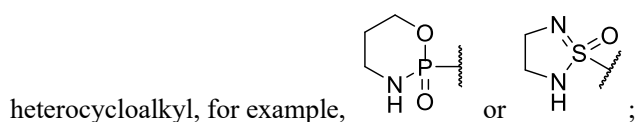
(35) in each R^{1-3} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(36) in each R^{1-3} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(37) in each R^{1-3} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;

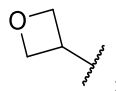
(38) in each R^{1-3-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

- (39) in each R^{1-3-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (40) in R^{1-4} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (41) in each R^{1-5} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (42) in each R^{1-5} , said C_3-C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclopentane; for example, cyclopropyl, cyclobutane or bicyclopentane;
- (43) in R^{1-5-1} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (44) A 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 is formed when the atom in R^1 is attached to the atom in A; said 5-10 membered heterocycloalkyl is 5-6 membered



- (45) in each R^0 , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (46) in R^2 , said 6-10 membered aryl is phenyl or naphthyl, for example, phenyl;
- (47) in R^2 , said 5-10 membered heteroaryl is 5 or 6 membered heteroaryl or 5-membered-fused 6-membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be one or more selected from N and/or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in said 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms is 2; the heteroatom in said 6 membered heteroaryl can be N, and the number of heteroatom(s) is 1 or 2; the heteroatom in said 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3;
- (48) in R^2 , said 4-10 membered heterocycloalkyl is a monocyclic, bridged, fused or spiro ring; said monocyclic ring can be 4-6 membered heterocycloalkyl; said fused ring can be 5-membered-fused 6-membered heterocycloalkyl or 4-membered-fused 6-membered heterocycloalkyl; said spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring or 4 membered-spiro 4-membered ring; the heteroatom in said 4-10 membered heterocycloalkyl can be selected from N and/or O, and the number of heteroatom(s) can be 1 or 2;
- (49) in R^2 , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (50) in each R^{2-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (51) in each R^{2-1} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

- (51) in each R^{2-1} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;
- (53) in each R^{2-1-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (54) in each R^{2-1-2} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (55) in each R^{2-1-3} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (56) in each R^{2-1-4} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (57) in each R^{2-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (58) in each R^{2-2} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;
- (59) in each R^{2-2-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (60) in each R^{2-2-2} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (61) in each R^{2-2-3} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (62) in each R^{2-3} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (63) in each R^{2-3} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (64) in each R^{2-3} , the heteroatom in said 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in said 3-6 membered heterocycloalkyl can also be O or N, and



the number of heteroatom(s) can also be 1; for example,

- (65) in each R^{2-3} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy or ethoxy;
- (66) in each R^{2-3-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (67) in each R^{2-3-1} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, and can be methoxy or ethoxy; in R^{2-3-2} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;
- (68) in each R^{2-3-3} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (69) in each R^{2-3} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be isopropyl;
- (70) in each R^{2-3-5} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

- (71) in each $R^{2-3-1-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (72) in each $R^{2-3-2-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (73) in each R^{2-4} , said 4-10 membered heterocycloalkyl is a monocyclic ring; said 4-10 membered heterocycloalkyl can be 4-6 membered heterocycloalkyl; the heteroatom in said 4-10 membered heterocycloalkyl can be selected from N and/or O, and the number of heteroatom(s) is 1 or 2;
- (75) in each R^{2-4} , said 5-10 membered heteroaryl is 5-membered-fused 6-membered heteroaryl; the heteroatom in said 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatom(s) is 1, 2 or 3;
- (76) in each R^{2-4} , said 6-10 membered aryl is phenyl or naphthyl, for example, phenyl;
- (77) in each R^{2-4} , said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopentyl;
- (78) in each R^{2-4-1} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (79) in each R^{2-4-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (80) in each R^{2-4-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (81) in each R^{2-4-2} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (82) in each R^{2-4-3} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (83) in each R^{2-4-3} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (84) in each R^{2-4-4} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;
- (85) in each R^{2-4-4} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (86) in $R^{2-4-1-1}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;
- (86) in each $R^{2-4-1-2}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;
- (88) in each R^{2-5} , said 4-10 membered heterocycloalkyl is a monocyclic ring; said 4-10 membered heterocycloalkyl can be 4-6 membered heterocycloalkyl; the heteroatom in said 4-10 membered heterocycloalkyl can be selected from N and/or O, and the number of heteroatom(s) can be 1 or 2;
- (89) in $R^{2-5-1-1}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;
- (90) in each $R^{2-5-1-2}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;
- (91) in R^{2-5-2} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,

pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;

(92) in each R^{2-6} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(93) in each R^{2-6} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(94) in each R^{2-6} , said 4-10 membered heterocycloalkyl is a monocyclic ring; said 4-10 membered heterocycloalkyl can be 4-6 membered heterocycloalkyl; the heteroatom in said 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1 or 2;

(95) in each R^{2-6} , said 5-10 membered heteroaryl is 5-6 membered heteroaryl; the heteroatom in said 5-6 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1 or 2;

(96) in each R^{2-6-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(97) in each R^{2-6-1} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(98) in $R^{2-6-1-1}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(99) in each R^{2-6-2} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;

(100) in each R^{2-6-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(101) in each R^{2-7} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(102) in each R^{2-7} , said 4-10 membered heterocycloalkyl can be a monocyclic or spiro ring; said monocyclic ring can be 4-6 membered heterocycloalkyl; said spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring or 4 membered-spiro 4-membered ring; the heteroatom in said 4-10 membered heterocycloalkyl can be selected from N and/or O, and the number of heteroatom(s) can be 1 or 2;

(103) in each R^{2-7} , said 5-10 membered heteroaryl is 5 or 6 membered heteroaryl or 5-membered-fused 6-membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be one or more selected from N and/or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in said 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms can be 2; the heteroatom in said 6 membered heteroaryl can be N, and the number of heteroatom(s) is 1 or 2; the heteroatom in said 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms can be 2, or the number of heteroatom(s) is 1, 2 or 3;

(104) in each R^{2-7-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(105) in each R^{2-7-1} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(106) in $R^{2-7-1-2}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl,

isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(107) in each R^{2-7-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(108) in each R^{2-7-2} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(109) in each R^{2-8} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(110) in each R^{2-8} , said 4-10 membered heterocycloalkyl is a monocyclic ring; said monocyclic ring can be 4-6 membered heterocycloalkyl; the heteroatom in said 4-10 membered heterocycloalkyl can be selected from N and/or O, and the number of heteroatom(s) can be 1 or 2;

(111) in each $R^{2-8-1-1}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(112) in R^3 , said 5-10 membered heteroaryl is 5 membered heteroaryl, 5-membered-fused 5-membered heteroaryl or 5-membered-fused 6-membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be one or more selected from N and/or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in said 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatom(s) can be 2; the heteroatom in said 5-membered-fused 6-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) can be 1, 2 or 3; the heteroatom in said 5-membered-fused 5-membered heteroaryl can be selected from N and/or O, and the number of heteroatoms can be 2;

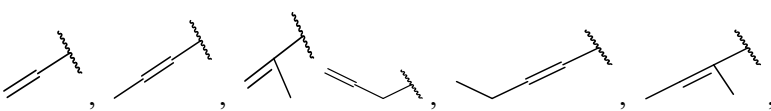
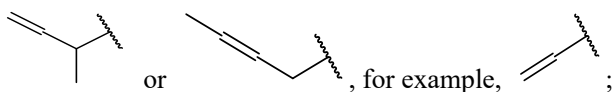
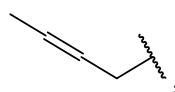
(113) in R^3 , said 3-10 membered heterocycloalkyl is a monocyclic ring; said monocyclic ring can be 4-6 membered heterocycloalkyl; the heteroatom in said 3-10 membered heterocycloalkyl can be selected from N, and the number of heteroatom(s) can be 1 or 2;

(114) in each R^{3-1} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(115) in each R^{3-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(116) in each R^{3-1-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(117) in R^{3-1-2} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or ethyl;

(118) in R^{3-1-2} , said C_2 - C_6 alkenyl is ,
 or , for example,  ;

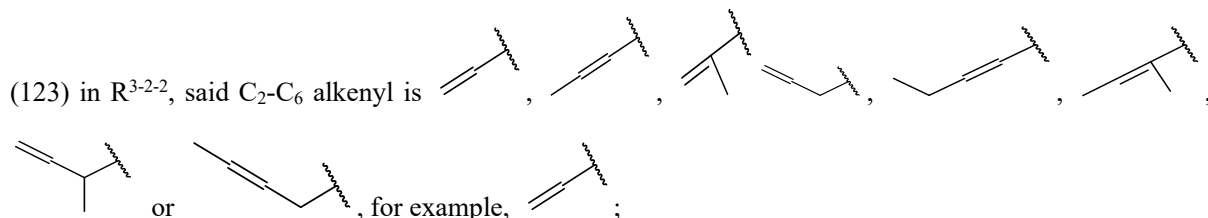
(119) in R^{3-2} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(120) in R^{3-2} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,

pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(121) in R^{3-2-1} , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(122) in R^{3-2-2} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;



(125) in R^4 , said halogen can be fluorine, chlorine, bromine or iodine, for example, fluorine;

(126) in R^4 , said 5-10 membered heterocycloalkyl is a spiro ring; said spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring, or 4 membered-spiro 4-membered ring; the heteroatom in said 4-10 membered heterocycloalkyl can be N, and the number of heteroatom(s) is 1 or 2;

(127) in R^4 , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(128) in each R^{4-2} , said 5-10 membered heteroaryl is 5 membered heteroaryl; the heteroatom in said 5 membered heteroaryl can be selected from N and/or S, and the number of heteroatoms can be 2;

(129) in R^{4-1-1} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl or isopropyl;

(130) in each R^{4-2-1} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(131) in each R^{4-2-1} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl;

(132) in $R^{1-2-5-1}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl or isopropyl;

and (133) in $R^{2-7-1-1}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl.

4. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 2, wherein the compound of formula I satisfies one or more of the following conditions:

(1) R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in said 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1;

(2) R^{1-2} is each independently selected from cyano or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} ;

(3) R^{1-2-1} is each independently halogen;

(4) R^{1-3} is each independently C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} ;

(5) R^{1-3-1} is each independently halogen;

(6) R^2 is hydrogen or 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 4-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2;

(7) R^{2-3} is each independently  ;

(8) R^{2-3-2} is C_1 - C_6 alkyl;

(9) R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{5-2} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heterocycloalkyl is N, O and S, and the number of heteroatom(s) is 1 or 2;

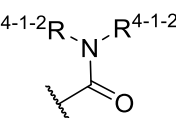
(10) R^{3-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{3-1-1} ;

(11) R^{3-1-1} is each independently halogen;

(12) R^{3-2} is each independently  ;

(13) R^{3-2-2} is C_1 - C_6 alkyl or C_2 - C_4 alkenyl;

(14) R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in said 5-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1, 2 or 3;

(15) R^{4-1} is each independently selected from  or  ;

(16) R^{4-1-1} is C_1 - C_6 alkyl;

and (17) R^{4-1-2} is each independently C_1 - C_6 alkyl.

5. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 2, wherein the compound of formula I satisfies one or more of the following conditions:

(1) R^1 is C_3 - C_6 cycloalkyl or 4 membered heterocycloalkyl, unsubstituted or substituted by one or more R^{1-2} ; the heteroatom in said 4 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1;

(2) R^2 is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

(3) R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 5-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in said 5-6 membered

heteroaryl is N and/or S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1;

(4) R^{3-2-2} is C_2-C_4 alkenyl;

and (5) R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in said 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2.

6. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 2, wherein the compound of formula I satisfies one or more of the following conditions:

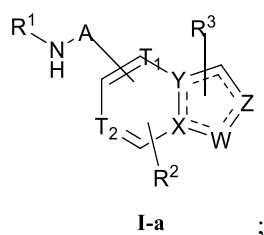
(1) R^1 is C_3-C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} ;

(2) R^2 is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

(3) R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

and (4) R^4 is 7-9 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in said 7-9 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1.

7. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 1, wherein the compound of formula I is a compound of formula I-a,



Y is C or N, X is C or N,

W is N, CH, O, NR^4 or CR^4 ;

Z is CH, O or N;

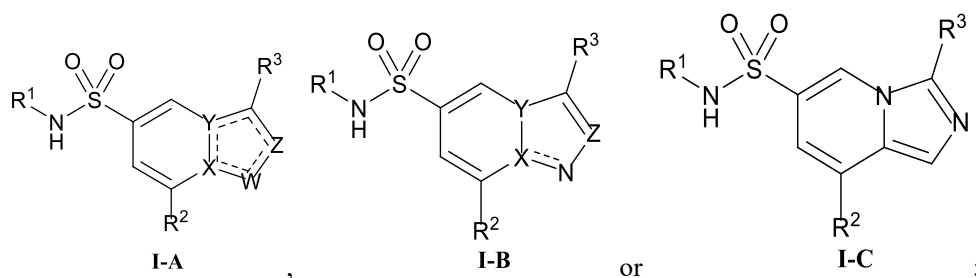
T_1 is C or N;

T_2 is C or N; and

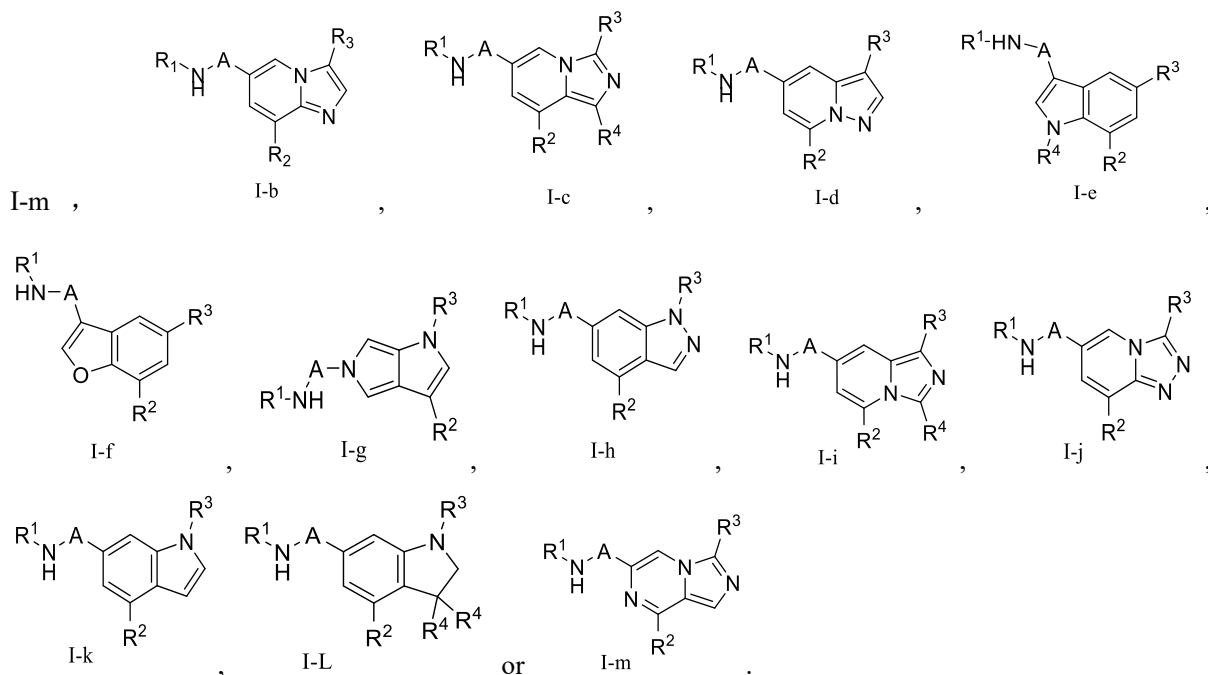
A, R^1 , R^2 , R^3 and R^4 are defined as in any one of claims 1-6.

8. The compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to claim 7, wherein at least one of T_1 , T_2 , X and Y is N, or Y, W and Z comprise only one heteroatom.

9. The compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to claim 1, wherein the compound of formula I-a can be a compound of formula I-A, I-B or I-C,



and/or, the compound of formula I is a compound of formula I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-L or



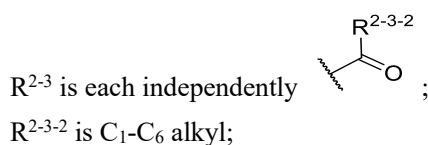
10. The compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to claim 2, wherein the compound of formula I is defined as in a scheme 1, a scheme 2, or a scheme 3;

in the scheme 1, R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in said 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1;

R^{1-2} is each independently selected from cyano or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} ; R^{1-2-1} is each independently halogen;

R^{1-3} is each independently C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} ; R^{1-3-1} is each independently halogen;

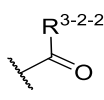
R^2 is hydrogen or 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 4-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2;



R³ is 5-10 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹ or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁵⁻²; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heterocycloalkyl is N, O and S, and the number of heteroatom(s) is 1 or 2;

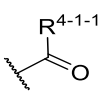
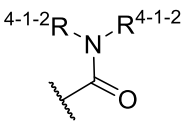
R³⁻¹ is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R³⁻² is each independently  ;

R³⁻²⁻² is C₁-C₆ alkyl or C₂-C₄ alkenyl;

R⁴ is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁴⁻¹; the heteroatom in said 5-10 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1, 2 or 3;

R⁴⁻¹ is each independently selected from  or  ;

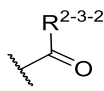
R⁴⁻¹⁻¹ is C₁-C₆ alkyl;

R⁴⁻¹⁻² is each independently C₁-C₆ alkyl;

in the scheme 2, R¹ is C₃-C₆ cycloalkyl or 4 membered heterocycloalkyl, unsubstituted or substituted by one or more R¹⁻²; the heteroatom in said 4 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1;

R¹⁻² is each independently selected from cyano or C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻²⁻¹; R¹⁻²⁻¹ is each independently halogen;

R² is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in said 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

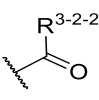
R²⁻³ is each independently  ;

R²⁻³⁻² is C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹ or 5-6 membered heterocycloalkyl unsubstituted or substituted by one or more R³⁻²; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1;

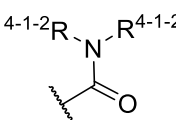
R³⁻¹ is each independently selected from halogen, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R^{3-2} is each independently  ;

R^{3-2-2} is C₂-C₄ alkenyl;

R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in said 5-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

R^{4-1} is each independently selected from  or  ;

R^{4-1-1} is C₁-C₆ alkyl;

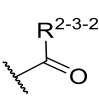
R^{4-1-2} is each independently C₁-C₆ alkyl;

in the scheme 3, R^1 is C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R^{1-2} ;

R^{1-2} is each independently selected from cyano or C₁-C₆ alkyl unsubstituted or substituted by one or more

R^{1-2-1} ; R^{1-2-1} is each independently halogen;

R^2 is hydrogen or 6-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 6-10 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1 or 2;

R^{2-3} is each independently  ;

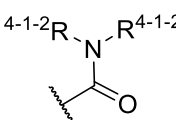
R^{2-3-2} is C₁-C₆ alkyl;

R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R^{3-1} is each independently selected from halogen, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R^{3-1-1} ;

R^{3-1-1} is each independently halogen;

R^4 is 7-9 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in said 7-9 membered heterocycloalkyl is N, and the number of heteroatom(s) is 1;

R^{4-1} is each independently selected from  or  ;

R^{4-1-1} is C₁-C₆ alkyl; and

R^{4-1-2} is each independently C₁-C₆ alkyl.

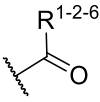
11. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 1, wherein the compound of formula I satisfies one or more of the following conditions:

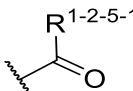
(1) R^1 is hydroxyl, C₁-C₆ alkyl unsubstituted or substituted by one or more R^{1-1} , C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R^{1-2} , 3-6 membered heterocycloalkyl unsubstituted or substituted

by one or more R^{1-3} ,  or amino unsubstituted or substituted by one or two R^{1-5} ; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{1-1} is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-1-1} , C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-1-2} or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-1-3} ; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R^{1-1-1} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-2} is each independently selected from deuterium, hydroxyl, cyano or halogen; R^{1-1-3} is each independently selected from deuterium, hydroxyl, cyano or halogen;

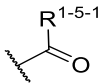
R^{1-2} is each independently selected from deuterium, hydroxyl, halogen, C_2 - C_6 alkynyl unsubstituted or substituted by one or more R^{1-2-2} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-2-3} , C_2 - C_6 alkenyl unsubstituted or substituted by one or more R^{1-2-4} , amino unsubstituted or substituted by one or two

R^{1-2-5} or ; $R^{1-2-2-1}$ is each independently halogen; R^{1-2-3} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-3-1}$; $R^{1-2-3-1}$ is each independently halogen; R^{1-2-4} is each independently selected from halogen, hydroxyl or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{1-2-4-1}$; $R^{1-2-4-1}$ is each independently halogen; R^{1-2-6} is each

independently amino; R^{1-2-5} is each independently ; $R^{1-2-5-1}$ is each independently C_1 - C_6 alkyl;

R^{1-3} is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} , C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-3-2} or C_2 - C_6 alkynyl; R^{1-3-1} is each independently halogen; R^{1-3-2} is each independently halogen;

R^{1-4} is C_1 - C_6 alkyl;

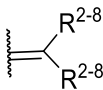
R^{1-5} is each independently selected from C_1 - C_6 alkyl,  or C_3 - C_6 cycloalkyl; R^{1-5-1} is C_1 - C_6 alkyl or amino;

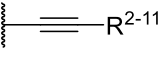
or, a 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 is formed when the atom in R_1 is attached to the atom in A; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from C_1 - C_6 alkyl or oxo;

(2) R^2 is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-1} , 5-10 membered

heteroaryl unsubstituted or substituted by one or more R^{2-2} , 4-12 membered heterocycloalkyl substituted by

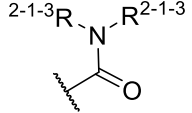
one or more R^{2-3} , , , C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{2-6} ,

, , C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{2-9} , C_3 - C_6 cycloalkenyl

unsubstituted or substituted by one or more R^{2-10} , or ; the heteroatom in said 5-10 membered

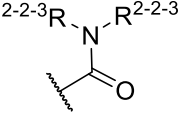
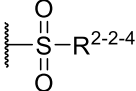
heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-1} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

more R^{2-1-1} , ,  or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{2-1-4} ;

R^{2-1-1} is each independently selected from cyano or halogen; R^{2-1-2} is hydrogen or C_1 - C_6 alkyl; R^{2-1-3} is each independently selected from hydrogen or C_1 - C_6 alkyl; R^{2-1-4} is each independently selected from halogen;

R^{2-2} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

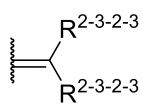
more R^{2-2-1} , , , C_1 - C_6 alkoxy or ;

R^{2-2-1} is each independently selected from cyano or halogen; R^{2-2-2} is hydrogen or C_1 - C_6 alkyl; R^{2-2-3} is each independently selected from hydrogen or C_1 - C_6 alkyl; R^{2-2-4} is each independently selected from C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl;

R^{2-3} is each independently selected from C_1 - C_6 alkyl substituted by one or more R^{2-3-1} , , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3-4} , amino unsubstituted or substituted by one or more R^{2-3-7} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-3-9} ; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-1} is each independently selected from cyano, or C_3 - C_6 cyano unsubstituted or substituted by one or more $R^{2-3-1-2}$;

R^{2-3-2} is hydrogen, or C_1 - C_6 alkyl substituted by one or more $R^{2-3-2-1}$, C_3 - C_6 cycloalkyl substituted by one or

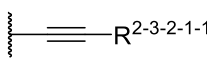
more $R^{2-3-2-2}$, , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-5}$, 5-10 membered heteroaryl unsubstituted or substituted by one or more $R^{2-3-2-6}$; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-4} is each independently C_1 - C_6 alkyl;

R^{2-3-7} is each independently C_1 - C_6 alkyl;

R^{2-3} is each independently selected from oxo or C_1 - C_6 alkyl;

$R^{2-3-1-2}$ is each independently C_1 - C_6 alkoxy; $R^{2-3-2-1}$ is each independently selected from hydroxyl, oxo,

, or 5-10 membered heteroaryl unsubstituted or substituted by one or more $R^{2-3-2-1-3}$; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

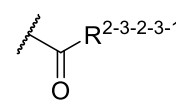
$R^{2-3-2-1-1}$ is each independently selected from C_1 - C_6 alkyl or 6-10 membered aryl; $R^{2-3-2-1-2}$ is each independently C_1 - C_6 alkyl; $R^{2-3-2-1-3}$ is each independently C_1 - C_6 alkyl;

$R^{2-3-2-2}$ is each independently selected from halogen, hydroxyl, C_1 - C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-2-1}$, C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$, or amino unsubstituted or substituted by one or more $R^{2-3-2-2-3}$;

$R^{2-3-2-2-1}$ is each independently selected from halogen or hydroxyl;

$R^{2-3-2-2-2}$ is each independently selected from halogen, deuterium, oxo or hydroxyl;

$R^{2-3-2-2-3}$ is each independently C_1 - C_6 alkyl;

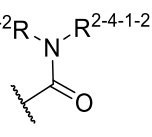
$R^{2-3-2-3}$ is each independently selected from hydrogen or ; $R^{2-3-2-3-1}$ is each independently 6-10 membered aryl unsubstituted or substituted by one or more $R^{2-3-2-3-1-1}$; $R^{2-3-2-3-1-1}$ is each independently C_1 - C_6 alkoxy;

$R^{2-3-2-4}$ is each independently halogen;

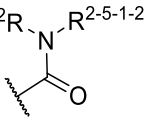
$R^{2-3-2-5}$ is each independently selected from halogen, hydroxyl, oxo, C_1 - C_6 alkoxy, or C_1 - C_6 alkyl substituted by one or more $R^{2-3-2-5-1}$; $R^{2-3-2-5-1}$ is each independently halogen;

$R^{2-3-2-6}$ is each independently C_1 - C_6 alkyl; R^{2-4} is 4-10 membered heterocycloalkyl substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , or 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the

heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-4-1} is each independently selected from hydroxyl, halogen, C_1-C_6 alkyl,  or  ;
 R^{2-4-2} is each independently selected from hydroxyl, halogen or C_1-C_6 alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or C_1-C_6 alkyl;

R^{2-5} is each independently selected from hydrogen, 4-10 membered heterocycloalkyl substituted by one or more R^{2-5-1} , , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-5-3} , or C_1-C_6 alkyl; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-5-1} is each independently selected from  or  ;

$R^{2-5-1-1}$ is hydrogen or C_1-C_6 alkyl;

$R^{2-5-1-2}$ is each independently selected from hydrogen or C_1-C_6 alkyl;

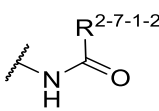
R^{2-5-2} is independently C_1-C_6 alkyl;

R^{2-5-3} is each independently C_1-C_6 alkoxy;

R^{2-6} is each independently selected from halogen, C_1-C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, C_1-C_6 alkyl or  ; $R^{2-6-1-1}$ is C_1-C_6 alkyl;
 R^{2-6-2} is each independently selected from halogen or C_1-C_6 alkyl;

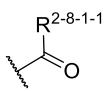
R^{2-7} is C_1-C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-7-1} is each independently selected from halogen, C_1-C_6 alkyl,  or  ; $R^{2-7-1-1}$ is

C₁-C₆ alkyl; R²⁻⁷⁻¹⁻² is C₁-C₆ alkyl;

R²⁻⁷⁻² is each independently selected from halogen or C₁-C₆ alkyl;

R²⁻⁸ is each independently C₁-C₆ alkyl, or two R²⁻⁸, together with the atoms to which they are attached, form a 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻⁸⁻¹; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻⁸⁻¹ is each independently ; R²⁻⁸⁻¹⁻¹ is hydrogen or C₁-C₆ alkyl;

R²⁻⁹ is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻⁹⁻¹; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻⁹⁻¹ is each independently C₁-C₆ alkyl;

R²⁻¹⁰ is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻¹⁰⁻¹; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

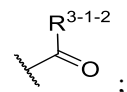
R²⁻¹⁰⁻¹ is each independently C₁-C₆ alkyl;

R²⁻¹¹ is each independently selected from 5-10 membered heteroaryl unsubstituted or substituted by one or more R²⁻¹¹⁻¹, or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻¹¹⁻²; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻¹¹⁻¹ is each independently C₁-C₆ alkyl; R²⁻¹¹⁻² is each independently C₁-C₆ alkyl;

(3) R³ is 5-10 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹ or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R³⁻²; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R³⁻¹ is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹ or



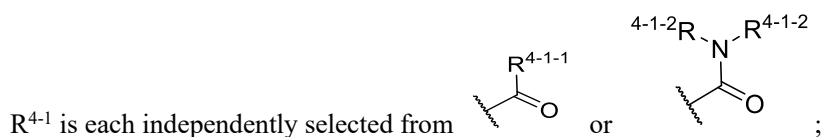
R³⁻¹⁻¹ is each independently selected from or hydroxyl; R³⁻¹⁻² is C₁-C₆ alkyl or C₂-C₆ alkenyl;

R³⁻² is each independently selected from hydroxyl, halogen, C₁-C₆ alkyl unsubstituted or substituted by one

or more R³⁻²⁻¹ or ;

R³⁻²⁻¹ is each independently halogen; R³⁻²⁻² is C₁-C₆ alkyl or C₂-C₄ alkenyl;

(4) R⁴ is deuterium, cyano, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁴⁻¹ or C₁-C₆ alkyl substituted by one or more R⁴⁻²; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;



R⁴⁻² is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R⁴⁻²⁻¹; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R⁴⁻¹⁻¹ is C₁-C₆ alkyl; R⁴⁻¹⁻² is each independently C₁-C₆ alkyl; R⁴⁻²⁻¹ is each independently C₁-C₆ alkyl.

12. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 2, wherein the compound of formula I satisfies one or more of the following conditions:

(1) R¹ is hydroxyl, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻², 3-6 membered heterocycloalkyl unsubstituted or substituted

by one or more R¹⁻³,  or amino unsubstituted or substituted by one or two R¹⁻⁵; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

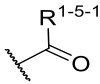
R¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano, halogen, 3-6 membered heterocycloalkyl, C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻¹⁻¹, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻¹⁻² or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻¹⁻³; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; R¹⁻¹⁻¹ is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻² is each independently selected from deuterium, hydroxyl, cyano or halogen; R¹⁻¹⁻³ is each independently selected from deuterium, hydroxyl, cyano or halogen;

R¹⁻² is each independently selected from deuterium, hydroxyl, halogen, C₂-C₆ alkynyl unsubstituted or substituted by one or more R¹⁻²⁻², C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻³, C₂-C₆ alkenyl unsubstituted or substituted by one or more R¹⁻²⁻⁴ or amino unsubstituted or substituted by one or two R¹⁻²⁻⁵; R¹⁻²⁻² is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻²⁻¹; R¹⁻²⁻²⁻¹ is each independently halogen; R¹⁻²⁻³ is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻³⁻¹; R¹⁻²⁻³⁻¹ is each independently halogen; R¹⁻²⁻⁴ is each independently selected from halogen, hydroxyl or C₁-C₆ alkoxy unsubstituted or substituted by one or more R¹⁻²⁻⁴⁻¹; R¹⁻²⁻⁴⁻¹ is each independently halogen;

R¹⁻³ is each independently selected from cyano, deuterium, hydroxyl, amino, halogen, C₁-C₆ alkyl

unsubstituted or substituted by one or more R^{1-3-1} or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{1-3-2} ; R^{1-3-1} is each independently halogen; R^{1-3-2} is each independently halogen;

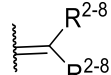
R^{1-4} is C_1 - C_6 alkyl;

R^{1-5} is each independently selected from C_1 - C_6 alkyl,  or C_3 - C_6 cycloalkyl;
 R^{1-5-1} is C_1 - C_6 alkyl or amino;

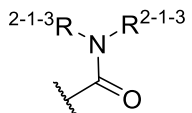
or, a 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^0 is formed when the atom in R_1 is attached to the atom in A; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O, P and S, and the number of heteroatom(s) is 3, 4 or 5; R^0 is each independently selected from C_1 - C_6 alkyl or oxo;

(2) R^2 is hydrogen, 6-10 membered aryl unsubstituted or substituted by one or more R^{2-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-2} , 4-10 membered heterocycloalkyl substituted by

one or more R^{2-3} , , , C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{2-6} ,

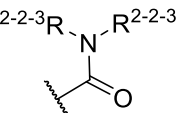
 or ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-1} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

more R^{2-1-1} , ,  or C_1 - C_6 alkoxy unsubstituted or substituted by one or more R^{2-1-4} ;

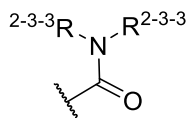
R^{2-1-1} is each independently selected from cyano or halogen; R^{2-1-2} is hydrogen or C_1 - C_6 alkyl; R^{2-1-3} is each independently selected from hydrogen or C_1 - C_6 alkyl; R^{2-1-4} is each independently selected from halogen;

R^{2-2} is each independently selected from cyano, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one or

more R^{2-2-1} , , or ;

R^{2-2-1} is each independently selected from cyano or halogen; R^{2-2-2} is hydrogen or C_1 - C_6 alkyl; R^{2-2-3} is each independently selected from hydrogen or C_1 - C_6 alkyl;

R^{2-3} is each independently selected from C_1 - C_6 alkyl substituted by one or more R^{2-3-1} , ,



, 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3-4} ; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3-1} is each independently cyano;

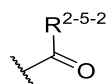
R^{2-3-2} is hydrogen; R^{2-3-4} is each independently $\text{C}_1\text{-C}_6$ alkyl;

R^{2-4} is 4-10 membered heterocycloalkyl substituted by one or more R^{2-4-1} , 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-4-2} , 6-10 membered aryl unsubstituted or substituted by one or more R^{2-4-3} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-4-1} is each independently selected from hydroxyl, halogen, $\text{C}_1\text{-C}_6$ alkyl, $\begin{array}{c} \text{R}^{2-4-1-1} \\ \diagdown \quad \diagup \\ \text{C}=\text{O} \end{array}$ or $\begin{array}{c} \text{R}^{2-4-1-2} \\ \diagdown \quad \diagup \\ \text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{O} \end{array}$;

R^{2-4-2} is each independently selected from hydroxyl, halogen or $\text{C}_1\text{-C}_6$ alkyl; R^{2-4-3} is each independently selected from hydroxyl, halogen or $\text{C}_1\text{-C}_6$ alkyl;

R^{2-5} is each independently hydrogen, 4-10 membered heterocycloalkyl substituted by one or more R^{2-5-1} , or



; the heteroatom in said 4-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-5-1} is each independently selected from $\begin{array}{c} \text{R}^{2-5-1-1} \\ \diagdown \quad \diagup \\ \text{C}=\text{O} \end{array}$ or $\begin{array}{c} \text{R}^{2-5-1-2} \\ \diagdown \quad \diagup \\ \text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{O} \end{array}$;

$\text{R}^{2-5-1-1}$ is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

$\text{R}^{2-5-1-2}$ is each independently selected from hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

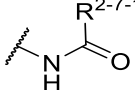
R^{2-5-2} is independently $\text{C}_1\text{-C}_6$ alkyl;

R^{2-6} is each independently selected from halogen, $\text{C}_1\text{-C}_6$ alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-6-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-6-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-6-1} is each independently selected from halogen, $\text{C}_1\text{-C}_6$ alkyl or $\begin{array}{c} \text{R}^{2-6-1-1} \\ \diagdown \quad \diagup \\ \text{C}=\text{O} \end{array}$; $\text{R}^{2-6-1-1}$ is $\text{C}_1\text{-C}_6$ alkyl;

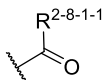
R^{2-6-2} is each independently selected from halogen or $\text{C}_1\text{-C}_6$ alkyl;

R^{2-7} is C_1 - C_6 alkyl, 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-7-1} or 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{2-7-2} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-7-1} is each independently selected from halogen, C_1 - C_6 alkyl,  or ; $R^{2-7-1-1}$ is C_1 - C_6 alkyl; $R^{2-7-1-2}$ is C_1 - C_6 alkyl;

R^{2-7-2} is each independently selected from halogen or C_1 - C_6 alkyl;

R^{2-8} is each independently C_1 - C_6 alkyl, or two R^{2-8} , together with the atoms to which they are attached, form a 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-8-1} ; the heteroatom in said 4-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-8-1} is each independently ; $R^{2-8-1-1}$ is hydrogen or C_1 - C_6 alkyl;

(3) R^3 is 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} or 3-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{3-2} ; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 3-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

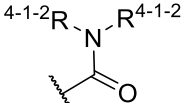
R^{3-1} is each independently selected from hydroxyl, halogen or ; R^{3-1-2} is C_1 - C_6 alkyl or C_2 - C_6 alkenyl;

R^{3-2} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkyl unsubstituted or substituted by one

or more R^{3-2-1} or ;

R^{3-2-1} is each independently halogen; R^{3-2-2} is C_1 - C_6 alkyl or C_2 - C_4 alkenyl;

R^4 is 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{4-2} ; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{4-1} is each independently selected from  or ;

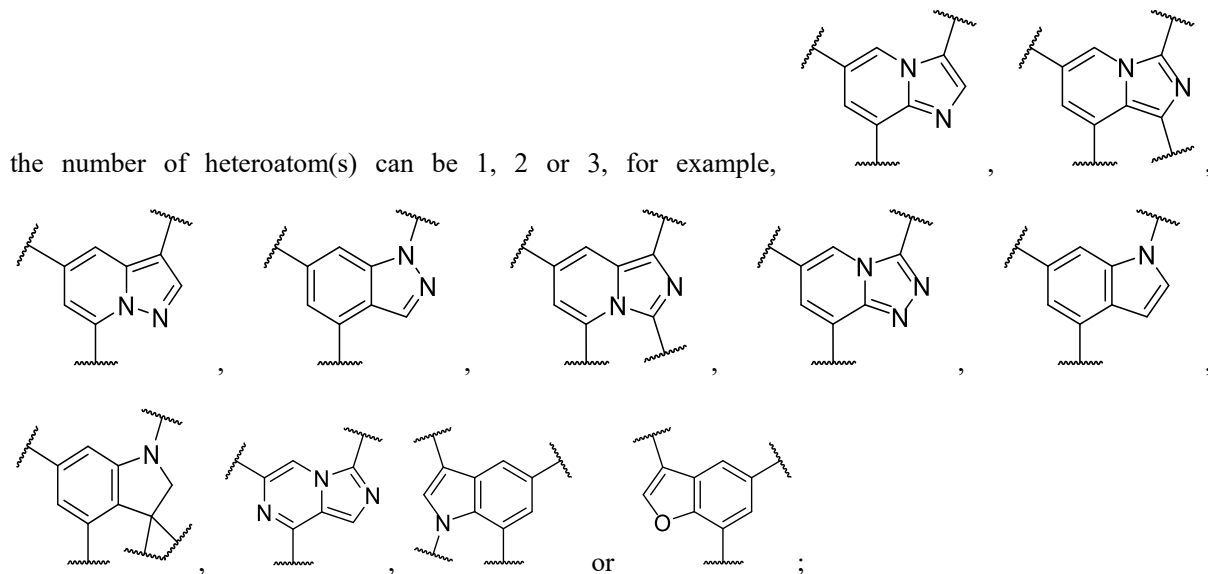
R^{4-2} is each independently 5-10 membered heteroaryl unsubstituted or substituted by one or more R^{4-2-1} ; the

heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; and

R^{4-1-1} is C_1 - C_6 alkyl; R^{4-1-2} is each independently C_1 - C_6 alkyl; R^{4-2-1} is each independently C_1 - C_6 alkyl.

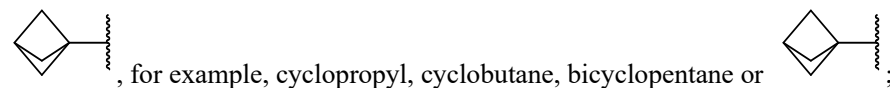
13. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 1, wherein the compound of formula I satisfies one or more of the following conditions:

(1) in ring B, the heteroatom in said 5-membered-fused 6-membered heteroaromatic ring is N and/or O, and

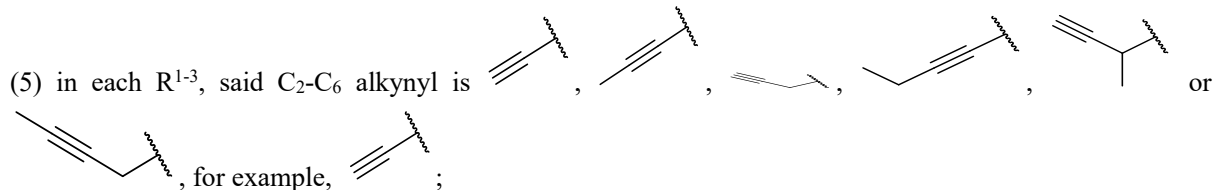
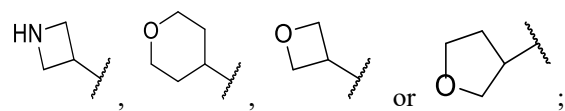


(2) in R^1 , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl, ethyl, isopropyl or tert-butyl;

(3) in R^1 , said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclopentane or



(4) in R^1 , the heteroatom in said 3-6 membered heterocycloalkyl is N, O or S, and the number of heteroatom(s) is 1 or 2; the heteroatom in said 3-6 membered heterocycloalkyl can be O or N, and the number of heteroatom can also be 1; azacyclobutane group, oxacyclobutane group, oxacyclo-azacyclobutanyl, oxacyclobutanyl, oxacyclopentanyl or oxacyclohexanyl is preferred, for example,

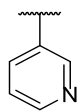


(6) in R^2 , said 5-10 membered heteroaryl is 5 or 6 membered heteroaryl, 5-membered-fused 5-membered

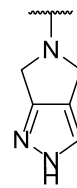
heteroaryl, or 5-membered-fused 6-membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5 membered heteroaryl can be N, the number of heteroatoms is 2, and pyrazolyl is preferred, for example,



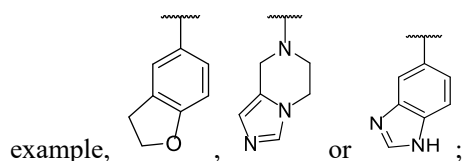
; the heteroatom in said 6 membered heteroaryl can be N, the number of heteroatom(s) is 1, and



pyridyl is preferred, for example, ; the heteroatom in said 5-membered-fused 5-membered heteroaryl



can be N, the number of heteroatoms is 3, dihydropyrrolopyrazolyl is preferred, for example, ; the heteroatom in said 5-membered-fused 6-membered heteroaryl can be N and/or O, the number of heteroatom(s) is 1, 2 or 3, and benzofuryl, dihydroimidazopyrazinyl or benzoimidazolyl is preferred, for

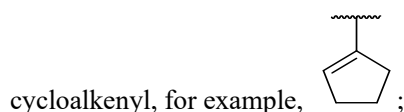


(7) in R^2 , said 4-12 membered heterocycloalkyl is one or more selected from a monocyclic ring, a bridged ring, a fused ring and a spiro ring; the heteroatom in said 4-12 membered heterocycloalkyl can be N and/or O, and the number of heteroatom(s) can be 1, 2 or 3; the heteroatom in said monocyclic ring can be 4-6 membered heterocycloalkyl; said fused ring can be 5-membered-fused 6-membered heterocycloalkyl, 4-membered-fused 6-membered heterocycloalkyl or 5-membered-fused 5-membered heterocycloalkyl; said spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring, 4 membered-spiro 4-membered ring, 5 membered-spiro 6-membered ring or 3 membered-spiro 6-membered ring; said bridged ring can be bicycloheterooctane or bicycloheteroheptane;

(8) in R^2 , said 4-12 membered heterocycloalkyl is saturated heterocycloalkyl, or heterocycloalkyl containing 1-2 double bond(s);

(9) in R^2 , said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopentyl;

(10) in R^2 , said C_3 - C_6 cycloalkenyl is cycloalkenyl containing 1 double bond, and can be 5 membered



(11) in each R^{2-2} , said C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy;

(12) in each $R^{2-2,4}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

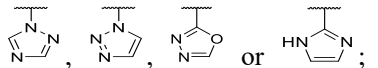
(13) in each $R^{2-2,4}$, said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl;

(14) in each R^{2-3} , said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, or can be methyl, ethyl, isopropyl or tert-butyl;

(15) in each R^{2-3} , said C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, or can be methoxy, ethoxy or isopropoxy;

(16) in each R^{2-3} , said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl;

(17) in each R^{2-3} , said 5-10 membered heteroaryl is 5 membered heteroaryl or 6 membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be N and/or O, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5 membered heteroaryl can be N and/or O, the number of heteroatoms can be 2 or 3,

and triazolyl, oxadiazolyl, or imidazolyl is preferred, for example, ; the heteroatom in said 6 membered heteroaryl can be N, the number of heteroatom(s) is 1 or 2, and pyridyl is

preferred, for example, .

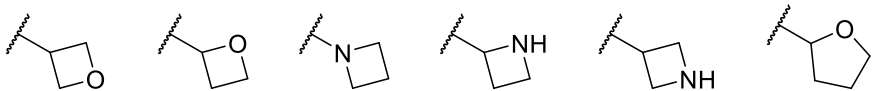
(18) in each $R^{2-3,1}$, said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl;

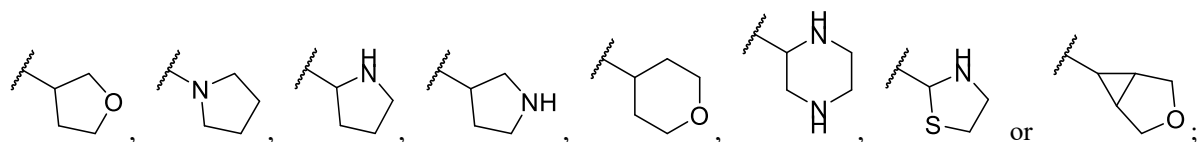
(19) in $R^{2-3,2}$, said C_1 - C_6 alkyl is C_1 - C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl, ethyl, isopropyl or tert-butyl;

(20) in $R^{2-3,2}$, said C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl or cyclobutyl;

(21) in $R^{2-3,2}$, said C_1 - C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, isopropoxy;

(22) in $R^{2-3,2}$, the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1 or 2; oxacyclobutanyl, azacyclobutanyl, oxacyclopentanyl, azacyclopentanyl, oxacyclohexanyl, azacyclohexanyl, pyrazinyl, thiazolidinyl or oxabicyclohexanyl is

preferred, for example, .



(23) in R^{2-3-2} , said 5-10 membered heteroaryl is 5 or 6 membered heteroaryl or 5-membered-fused 6-membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be N and/or O, and the number of heteroatom(s) can be 1 or 2; the heteroatom in said 5 membered heteroaryl can be N and/or O, and the number of heteroatom(s) is 2; the heteroatom in said 6 membered heteroaryl can be N, and the number of heteroatom(s) is 1; the heteroatom in said 5-membered-fused 6-membered heteroaryl can be O, and the number of heteroatoms is 2;

(24) in each R^{2-3-3} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl or ethyl;

(25) in each R^{2-3-6} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(26) in each R^{2-3-7} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(27) in each R^{2-3-8} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl or isopropyl;

(28) in each R^{2-3-8} , said C_3-C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, for example, cyclopropyl;

(29) in each R^{2-3-9} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(30) in each $R^{2-3-1-2}$, said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy;

(31) in each $R^{2-3-1-3}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(32) in each $R^{2-3-2-1}$, said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy;

(33) in each $R^{2-3-2-1}$, said 5-10 membered heteroaryl is 5 membered heteroaryl; the heteroatom in said 5 membered heteroaryl can be N, and the number of heteroatoms is 3;

(34) in each $R^{2-3-2-1-1}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(35) in each $R^{2-3-2-1-1}$, said 6-10 membered aryl is phenyl or naphthyl, for example, phenyl;

(36) in each $R^{2-3-2-1-2}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(37) in each $R^{2-3-2-1-3}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl,

isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(38) in each $R^{2-3-2-2}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(39) in each $R^{2-3-2-2}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(40) in each $R^{2-3-2-2}$, said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy, ethoxy or n-propoxy;

(41) in each $R^{2-3-2-2-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(42) in each $R^{2-3-2-2-2}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(43) in each $R^{2-3-2-2-3}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(44) in each $R^{2-3-2-3-1}$, said 6-10 membered aryl is phenyl or naphthyl, for example, phenyl;

(45) in each $R^{2-3-2-3-1-1}$, said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy;

(46) in each $R^{2-3-2-4}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(47) in each $R^{2-3-2-5}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(48) in each $R^{2-3-2-5}$, said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy;

(49) in each $R^{2-3-2-5}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl, ethyl, n-propyl or isopropyl;

(50) in each $R^{2-3-2-5-1}$, said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine;

(51) in each $R^{2-3-2-6}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(52) in each $R^{2-3-3-1-1}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

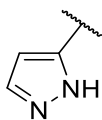
(53) in each R^{2-5} , said 6-10 membered aryl is phenyl or naphthyl, for example, phenyl;

(54) in each R^{2-5} , said C_1-C_6 alkyl is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(55) in each $R^{2-5-1-1}$, said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl or isopropyl;

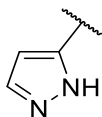
(56) in each R^{2-5-3} , said C_1-C_6 alkoxy is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, pr-butoxy, sec-butoxy or tert-butoxy, for example, methoxy;

(57) in each R^{2-9} , said 5-10 membered heteroaryl is 5 membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be N and/or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in said 5 membered heteroaryl can be N, and the number of heteroatoms is 2; pyrazolyl is preferred, for



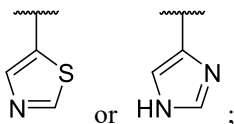
example, ;

(58) in each R^{2-10} , said 5-10 membered heteroaryl is 5 membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be N and/or S, and the number of heteroatom(s) can be 1 or 2; the heteroatom in said 5 membered heteroaryl can be N, and the number of heteroatoms is 2; pyrazolyl is preferred, for



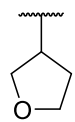
example, ;

(59) in each R^{2-11} , said 5-10 membered heteroaryl is 5 membered heteroaryl; the heteroatom in said 5 membered heteroaryl can be N and/or S, and the number of heteroatoms is 2; thiazolyl or imidazolyl is



preferred, for example, or ;

(60) in each R^{2-11} , the heteroatom in said 3-6 membered heterocycloalkyl is O, and the number of



heteroatom(s) can be 1; oxacyclopentanyl is preferred, for example, ;

(61) in each R^{2-11-1} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(62) in each R^{2-11-2} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl;

(63) in R^3 , said 5-10 membered heteroaryl is 5 membered heteroaryl, 5-membered-fused 5-membered heteroaryl or 5-membered-fused 6-membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl can be N and/or S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5 membered heteroaryl can be N and/or S, and the number of heteroatom(s) is 2 or 3; the heteroatom in said 5-membered-fused 6-membered heteroaryl can be N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-membered-fused 5-membered heteroaryl can be N and/or O, and the number of heteroatoms is 2, or the number of heteroatom(s) is 1, 2 or 3;

(64) in R^{3-2-2} , said C_1-C_6 alkyl is C_1-C_4 alkyl, and can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pr-butyl, sec-butyl or tert-butyl, for example, methyl or ethyl;

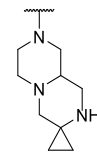
(65) in R^4 , said halogen is fluorine, chlorine, bromine or iodine, for example, fluorine or chlorine; and

(66) in R^4 , said 4-10 membered heterocycloalkyl is a monocyclic or spiro ring; said monocyclic ring can be 6 membered heterocycloalkyl; said spiro ring can be 4 membered-spiro 6-membered ring, 4 membered-spiro 5-membered ring or 4 membered-spiro 4-membered ring; the heteroatom in said 4-10 membered

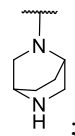
heterocycloalkyl can be N, and the number of heteroatom(s) is 1 or 2.

14. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 13, wherein the compound of formula I satisfies one or more of the following conditions:

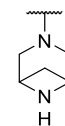
(1) said 4-12 membered heterocycloalkyl is 3-membered-spiro6-membered-fused 6-membered



heterocycloalkyl, preferably, hexahydro-spiro-cyclopropan-pyrazinopyrazinyl, for example,

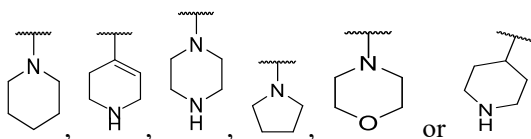


(2) said bicycloheterooctane is bicyclo[2.2.2]heterooctane, for example,



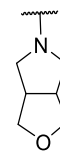
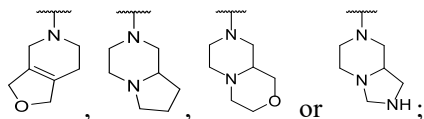
(3) said bicycloheteroheptane is bicyclo[3.1.1]heteroheptane, for example,

(4) said 4-6 membered heterocycloalkyl is azacyclohexanyl, tetrahydropyridyl, piperazinyl,



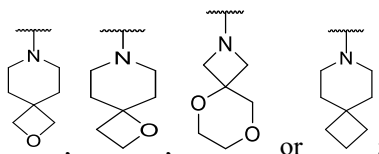
azacyclopentanyl or morpholinyl, for example,

(5) said 5-membered-fused 6-membered heterocycloalkyl is tetrahydrofuranopyridyl, hexahydropyrrolopyrazinyl, hexahydropyrazinooxazinyl or hexahydroimidazopyrazinyl, for example,

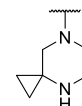


(6) said 5-membered-fused 5-membered heterocycloalkyl is tetrahydrofuranopyrrolyl, for example,

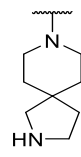
(7) said 4 membered-spiro 6-membered ring is oxaaza-spiro-nonanyl, dioxaza-spiro-nonanyl or



aza-spiro-nonanyl, for example,



(8) said 3 membered-spiro 6-membered ring is diaza-spiro-octanyl, for example,



(9) said 5 membered-spiro 6-membered ring is diaza-spiro-decanyl, for example,

15. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 1, wherein the compound of formula I satisfies one or more of the following conditions:

(1) R^1 is C_3 - C_6 cycloalkyl substituted by one or more R^{1-2} , or 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

(2) R^{1-2} is each independently C_2 - C_6 alkynyl;

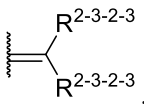
(3) R^{1-3} is each independently selected from cyano, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} , or C_2 - C_6 alkynyl;

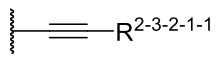
(4) R^{1-3-1} is each independently halogen;

(5) R^2 is 4-12 membered heterocycloalkyl substituted by one or more R^{2-3} ; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O, and S, and the number of heteroatom(s) is 1, 2 or 3;

(6) R^{2-3} is each independently selected from , or 5-10 membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl is N and/or O, and the number of heteroatoms is 2 or 3;

(7) R^{2-3-2} is C_1 - C_6 alkyl substituted by one or more $R^{2-3-2-1}$, C_3 - C_6 cycloalkyl unsubstituted or substituted by

one or more $R^{2-3-2-2}$, , 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-5}$, or 5-10 membered heteroaryl; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is selected from N and/or O, and the number of heteroatom(s) is 1 or 2;

(8) $R^{2-3-2-1}$ is each independently selected from hydroxyl, or ; ;

(9) $R^{2-3-2-1-1}$ is each independently C_1 - C_6 alkyl;

(10) $R^{2-3-2-2}$ is each independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$, or amino;

(11) $R^{2-3-2-2-2}$ is each independently deuterium;

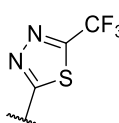
(12) $R^{2-3-2-3}$ is each independently selected from hydrogen or  $R^{2-3-2-3-1}$;

(13) $R^{2-3-2-3-1}$ is each independently 6-10 membered aryl unsubstituted or substituted by one or more $R^{2-3-2-3-1-1}$; $R^{2-3-2-3-1-1}$ is each independently C_1 - C_6 alkoxy;

(14) $R^{2-3-2-5}$ is each independently selected from halogen, C_1 - C_6 alkoxy, or C_1 - C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-5-1}$;

(15) $R^{2-3-2-5-1}$ is each independently halogen;

(16) R^3 is unsubstituted 5-6 membered heteroaryl; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

(17) R^3 is  ;

(18) R^4 is deuterium, cyano, 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} s; a heteroatom in the 5-10 membered heterocycloalkyl is one or more selected from N, O, and S, and a heteroatom number is 1 or 2; and

(19) R^{4-1} is each independently  R^{4-1-1} ; and R^{4-1-1} is C_1 - C_6 alkyl.

16. The compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to claim 1, wherein the compound of formula I is defined as in a scheme 4, a scheme 5, a scheme 6, a scheme 7, a scheme 8, a scheme 9, a scheme 10 or a scheme 11:

in a solution 4,

R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} ;

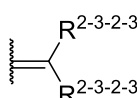
R^{1-2} is each independently selected from cyano, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} , or C_2 - C_6 alkynyl;

R^{1-2-1} is each independently selected from deuterium, halogen, or hydroxyl;

R^2 is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 4-10 membered heterocycloalkyl is N and/or O, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3} is each independently selected from  R^{2-3-2} , or 5-10 membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl is N and/or O, and the number of heteroatoms is 2 or 3;

R^{2-3-2} is C_1 - C_6 alkyl substituted by one or more $R^{2-3-2-1}$, C_3 - C_6 cycloalkyl unsubstituted or substituted by one

or more $R^{2-3-2-2}$,  $R^{2-3-2-3}$, 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more

$R^{2-3-2-5}$, or 5-10 membered heteroaryl; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

$R^{2-3-2-1}$ is each independently selected from hydroxyl, or  $\equiv R^{2-3-2-1-1}$;

$R^{2-3-2-1-1}$ is each independently C_1 - C_6 alkyl;

$R^{2-3-2-2}$ is each independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$, or amino;

$R^{2-3-2-2-2}$ is each independently deuterium;

$R^{2-3-2-3}$ is each independently selected from hydrogen or  $R^{2-3-2-3-1}$;

$R^{2-3-2-3-1}$ is each independently 6-10 membered aryl unsubstituted or substituted by one or more $R^{2-3-2-3-1-1}$;

$R^{2-3-2-3-1-1}$ is each independently C_1 - C_6 alkoxy;

$R^{2-3-2-5}$ is each independently selected from halogen, C_1 - C_6 alkoxy, or C_1 - C_6 alkyl unsubstituted or substituted by one or more $R^{2-3-2-5-1}$;

$R^{2-3-2-5-1}$ is each independently halogen;

R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R^{3-1} is each independently C_1 - C_6 alkyl substituted by one or more R^{3-1-1} ;

R^{3-1-1} is each independently halogen;

R^4 is hydrogen, cyano, halogen, C_1 - C_6 alkyl, or 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{4-1} ; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1 or 2;

R^{4-1} is each independently  R^{4-1-1} ; R^{4-1-1} is C_1 - C_6 alkyl; in the scheme 5,

R^1 is C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more R^{1-2} ;

R^{1-2} is each independently selected from cyano, or C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-2-1} ;

R^{1-2-1} is each independently selected from deuterium or halogen;

R^2 is 4-10 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 4-10 membered heterocycloalkyl is N and/or O, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3} is each independently  R^{2-3-2} ;

R^{2-3-2} is C_3 - C_6 cycloalkyl substituted by one or more $R^{2-3-2-2}$, or 3-6 membered heterocycloalkyl substituted by one or more $R^{2-3-2-5}$; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; the heteroatom in said 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

$R^{2-3-2-2}$ is each independently selected from C_1 - C_6 alkyl, or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$;

$R^{2-3-2-2-2}$ is each independently deuterium;

$R^{2-3-2-5}$ is each independently C_1 - C_6 alkyl;

R^3 is 5-6 membered heteroaryl unsubstituted or substituted by one or more R^{3-1} ; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R^{3-1} is each independently C_1 - C_6 alkyl substituted by one or more R^{3-1-1} ;

R^{3-1-1} is each independently halogen;

R^4 is hydrogen, cyano, or C_1 - C_6 alkyl;

in the scheme 6,

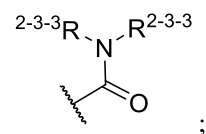
R^1 is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R^{1-3} ; the heteroatom in said 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1;

R^{1-3} is each independently selected from cyano, C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{1-3-1} , or C_2 - C_6 alkynyl;

R^{1-3-1} is each independently selected from halogen or deuterium;

R^2 is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R^{2-3} ; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O, and S, and the number of heteroatom(s) is 1, 2 or 3;

R^{2-3} is each independently C_1 - C_6 alkyl unsubstituted or substituted by one or more R^{2-3-1} , , or



R^{2-3-1} is each independently selected from hydroxyl, halogen, C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-1-1}$, or amino unsubstituted or substituted by one or more $R^{2-3-1-3}$;

$R^{2-3-1-1}$ is each independently deuterium;

$R^{2-3-1-3}$ is each independently C_1 - C_6 alkyl;

R^{2-3-2} is C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl unsubstituted or substituted by one or more $R^{2-3-2-2}$;

$R^{2-3-2-2}$ is each independently selected from C_1 - C_6 alkyl, or C_1 - C_6 alkoxy unsubstituted or substituted by one or more $R^{2-3-2-2-2}$;

$R^{2-3-2-2-2}$ is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl;

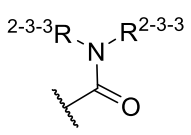
in the scheme 7,

R¹ is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R¹⁻³; the heteroatom in said 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1;

R¹⁻³ is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹, or C₂-C₆ alkynyl;

R¹⁻³⁻¹ is each independently halogen;

R² is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O, and S, and the number of heteroatom(s) is 1, 2 or 3;

R²⁻³ is each independently C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻¹, , or  ;

R²⁻³⁻¹ is each independently selected from hydroxyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹;

R²⁻³⁻¹⁻¹ is each independently deuterium;

R²⁻³⁻² is C₁-C₆ alkyl, or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻²;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in said 5-6

membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl;

in a solution 8,

R¹ is C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻²;

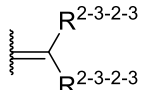
R¹⁻² is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻²⁻¹, or C₂-C₆ alkynyl;

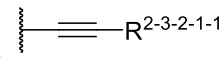
R¹⁻²⁻¹ is each independently selected from deuterium, halogen, or hydroxyl;

R² is 4-10 membered heterocycloalkyl substituted by one or more R²⁻³; the heteroatom in said 4-10 membered heterocycloalkyl is N and/or O, and the number of heteroatom(s) is 1, 2 or 3; said 4-10 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring, a 7-10 membered saturated spiro ring or a 7-10 membered saturated bridged ring;

R²⁻³ is each independently selected from  R²⁻³⁻², or 5-10 membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl is N and/or O, and the number of heteroatoms is 2 or 3;

R²⁻³⁻² is C₁-C₆ alkyl substituted by one or more R²⁻³⁻²⁻¹, C₃-C₆ cycloalkyl unsubstituted or substituted by one

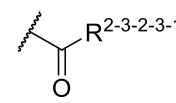
or more R²⁻³⁻²⁻²,  R²⁻³⁻²⁻³, 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻⁵, or 5-10 membered heteroaryl; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; said 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring; the heteroatom in said 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

R²⁻³⁻²⁻¹ is each independently selected from hydroxyl, or  R²⁻³⁻²⁻¹⁻¹ ;

R²⁻³⁻²⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R²⁻³⁻²⁻² is each independently selected from halogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻², or amino;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻²⁻³ is each independently selected from hydrogen or  R²⁻³⁻²⁻³⁻¹ ;

R²⁻³⁻²⁻³⁻¹ is each independently 6-10 membered aryl unsubstituted or substituted by one or more R²⁻³⁻²⁻³⁻¹⁻¹;

R²⁻³⁻²⁻³⁻¹⁻¹ is each independently C₁-C₆ alkoxy;

R²⁻³⁻²⁻⁵ is each independently selected from halogen, C₁-C₆ alkoxy, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻⁵⁻¹;

R²⁻³⁻²⁻⁵⁻¹ is each independently halogen;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen; and

R⁴ is hydrogen, cyano, halogen, C₁-C₆ alkyl, or 5-10 membered heterocycloalkyl unsubstituted or substituted by one or more R⁴⁻¹; the heteroatom in said 5-10 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1 or 2; said 5-10 membered heterocycloalkyl is a 7-10 membered unsaturated spiro ring;

R⁴⁻¹ is each independently ; R⁴⁻¹⁻¹ is C₁-C₆ alkyl; in a solution 9,

R¹ is C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R¹⁻²;

R¹⁻² is each independently selected from cyano, or C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻²⁻¹;

R¹⁻²⁻¹ is each independently selected from deuterium or halogen;

R² is 4-10 membered heterocycloalkyl substituted by one or more R²⁻³; the heteroatom in said 4-10 membered heterocycloalkyl is selected from N and/or O, and the number of heteroatom(s) is 1, 2 or 3; said 4-10 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring or a 7-10 membered saturated spiro ring;

R²⁻³ is each independently ;

R²⁻³⁻² is C₃-C₆ cycloalkyl substituted by one or more R²⁻³⁻²⁻², 3-6 membered heterocycloalkyl substituted by one or more R²⁻³⁻²⁻⁵; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; said 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring; the heteroatom in said 5-10 membered heteroaryl is N and/or O, and the number of heteroatom(s) is 1 or 2;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻²⁻⁵ is each independently C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R⁴ is hydrogen, cyano, or C₁-C₆ alkyl;

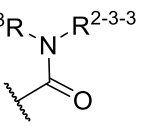
in a solution 10,

R¹ is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R¹⁻³; the heteroatom in said 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1; said 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring;

R¹⁻³ is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹, or C₂-C₆ alkynyl;

R¹⁻³⁻¹ is each independently selected from halogen or deuterium;

R² is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; said 4-12 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring, a 7-10 membered saturated fused ring or a 7-10 membered saturated spiro ring;

R²⁻³ is each independently C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻¹, , or  ;

R²⁻³⁻¹ is each independently selected from hydroxyl, halogen, C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹, or amino unsubstituted or substituted by one or more R²⁻³⁻¹⁻³;

R²⁻³⁻¹⁻¹ is each independently deuterium;

R²⁻³⁻¹⁻³ is each independently C₁-C₆ alkyl;

R²⁻³⁻² is C₁-C₆ alkyl, or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻²;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen;

R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl;

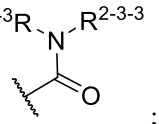
in a solution 11,

R¹ is 3-6 membered heterocycloalkyl unsubstituted or substituted by one or more R¹⁻³; the heteroatom in said 3-6 membered heterocycloalkyl is O, and the number of heteroatom(s) is 1; said 3-6 membered heterocycloalkyl is a 3-6 membered saturated monocyclic ring;

R¹⁻³ is each independently selected from cyano, C₁-C₆ alkyl unsubstituted or substituted by one or more R¹⁻³⁻¹, or C₂-C₆ alkynyl;

R¹⁻³⁻¹ is each independently halogen;

R² is 4-12 membered heterocycloalkyl unsubstituted or substituted by one or more R²⁻³; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3; said 4-12 membered heterocycloalkyl is a 4-6 membered saturated monocyclic ring, a 7-10 membered saturated fused ring or a 7-10 membered saturated spiro ring;

R²⁻³ is each independently C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻¹, , or  ;

R²⁻³⁻¹ is each independently selected from hydroxyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻¹⁻¹;

R²⁻³⁻¹⁻¹ is each independently deuterium;

R²⁻³⁻² is C₁-C₆ alkyl, or C₃-C₆ cycloalkyl unsubstituted or substituted by one or more R²⁻³⁻²⁻²;

R²⁻³⁻²⁻² is each independently selected from C₁-C₆ alkyl, or C₁-C₆ alkoxy unsubstituted or substituted by one or more R²⁻³⁻²⁻²⁻²;

R²⁻³⁻²⁻²⁻² is each independently deuterium;

R²⁻³⁻³ is each independently selected from hydrogen, or C₁-C₆ alkyl unsubstituted or substituted by one or more R²⁻³⁻³⁻¹;

R²⁻³⁻³⁻¹ is each independently amino unsubstituted or substituted by one or more R²⁻³⁻³⁻¹⁻¹;

R²⁻³⁻³⁻¹⁻¹ is each independently C₁-C₆ alkyl;

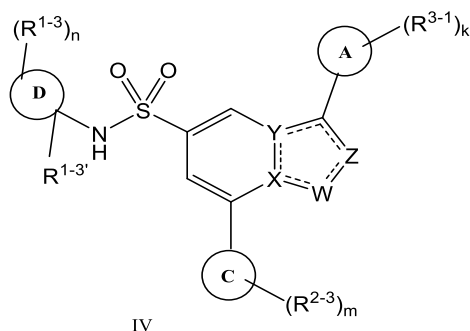
R³ is 5-6 membered heteroaryl unsubstituted or substituted by one or more R³⁻¹; the heteroatom in said 5-6 membered heteroaryl is N and/or S, and the number of heteroatoms is 3;

R³⁻¹ is each independently C₁-C₆ alkyl substituted by one or more R³⁻¹⁻¹;

R³⁻¹⁻¹ is each independently halogen; and

R⁴ is hydrogen, deuterium, halogen, or C₁-C₆ alkyl.

17. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 7, wherein the compound of formula I-a can be a compound of formula IV,



ring D is 3-6 membered heterocycloalkyl; the heteroatom in said 3-6 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

ring C is 4-12 membered heterocycloalkyl; the heteroatom in said 4-12 membered heterocycloalkyl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

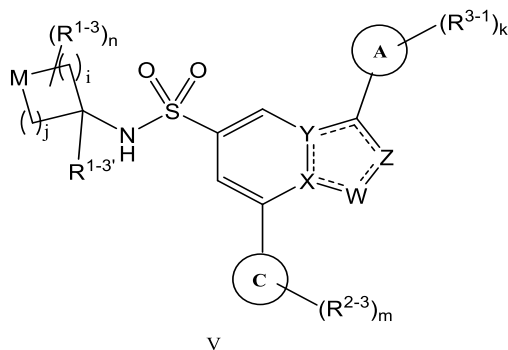
ring A is 5-10 membered heteroaryl; the heteroatom in said 5-10 membered heteroaryl is one or more selected from N, O and S, and the number of heteroatom(s) is 1, 2 or 3;

n is 0, 1 or 2; m is 0, 1 or 2; k is 0, 1 or 2;

R^{1-3'} is hydrogen or R¹⁻³; and

R¹⁻³, R²⁻³ and R³⁻¹ are defined as in any one of claims 1-6 and 11-16.

18. The compound of formula I, the pharmaceutically acceptable salt thereof, or the isotopic compound thereof according to claim 17, wherein the compound of formula I-a can be a compound of formula V,

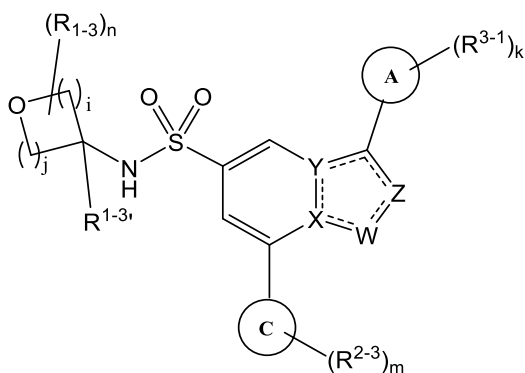


M is N, O or S;

i is 0, 1 or 2; j is 0, 1 or 2; i and j are not 0 at the same time;

ring C, ring A, R^{1-3'}, R¹⁻³, R²⁻³, R³⁻¹, n, m and k are defined as in claim 17;

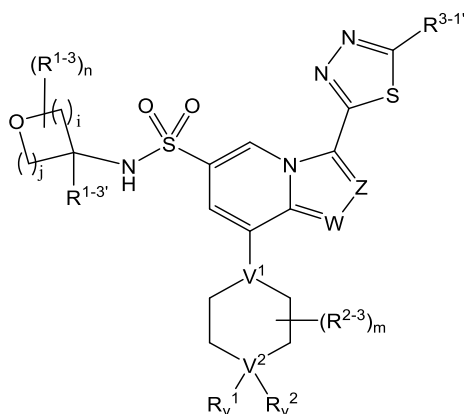
more preferably, the compound of formula I-a can be a compound represented by formula VI,



VI

ring C, ring A, $R^{1-3'}$, R^{1-3} , R^{2-3} , R^{3-1} , n , m , k , i and j are defined as in claim 17;

most preferably, the compound of formula I-a can be a compound represented by formula VII,



VII

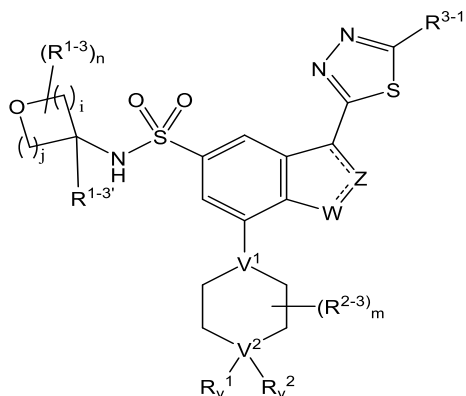
V^1 is CH, N or O; V^2 is CH, N or O; V^1 and V^2 are not CH at the same time;

$R^{3-1'}$ is hydrogen or R^{3-1} ; and

R_{V^1} is hydrogen or R^{2-3} ; R_{V^2} is hydrogen or R^{2-3} ;

$R^{1-3'}$, R^{1-3} , R^{2-3} , R^{3-1} , n , m , i and j are defined as in claim 17;

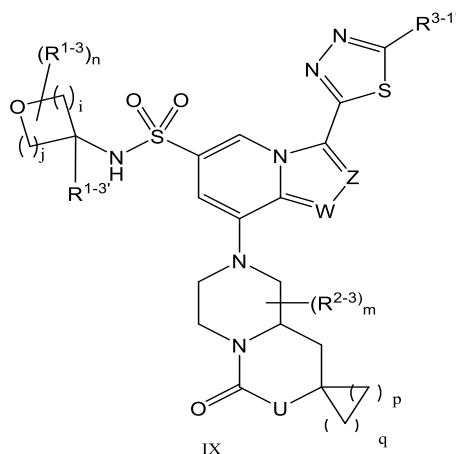
or, the compound of formula I-a can be a compound represented by formula VIII,



VIII

R_{V^1} , R_{V^2} , $R^{1-3'}$, R^{1-3} , R^{2-3} , $R^{3-1'}$, n , m , i and j are defined as in claim 17;

most preferably, the compound of formula I-a can be a compound represented by formula IX,

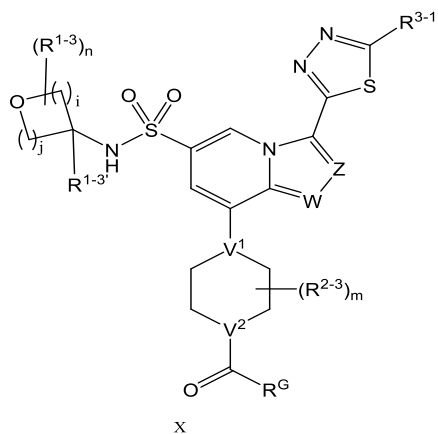


U is CH, N or O;

p is 0, 1 or 2; q is 0, 1 or 2;

$R^{1-3'}$, R^{1-3} , R^{2-3} , $R^{3-1'}$, n, m, i and j are defined as in claim 17;

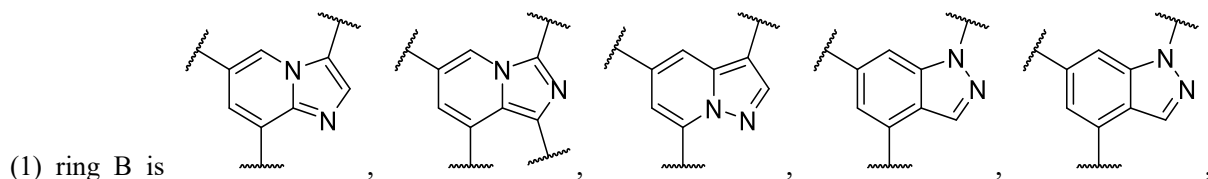
or, the compound of formula I-a can be a compound represented by formula X,

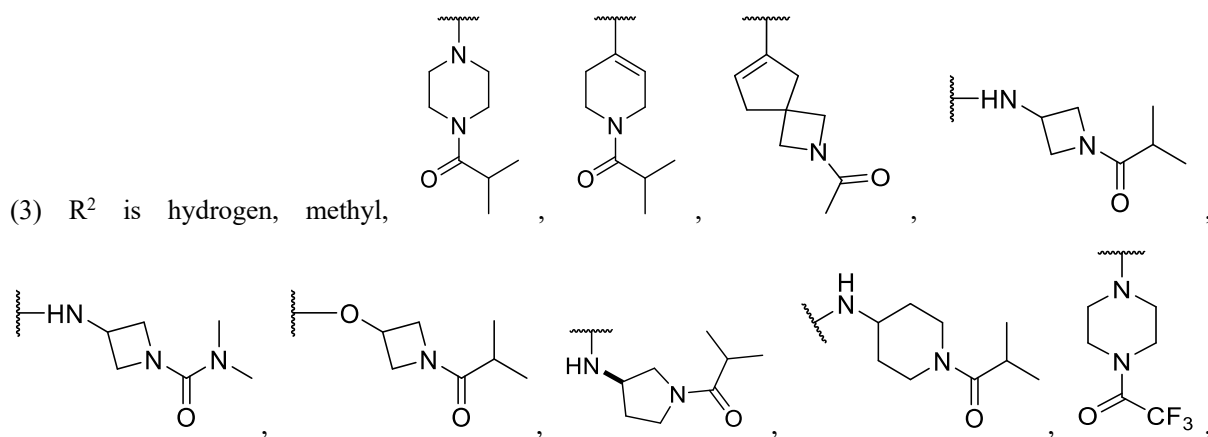
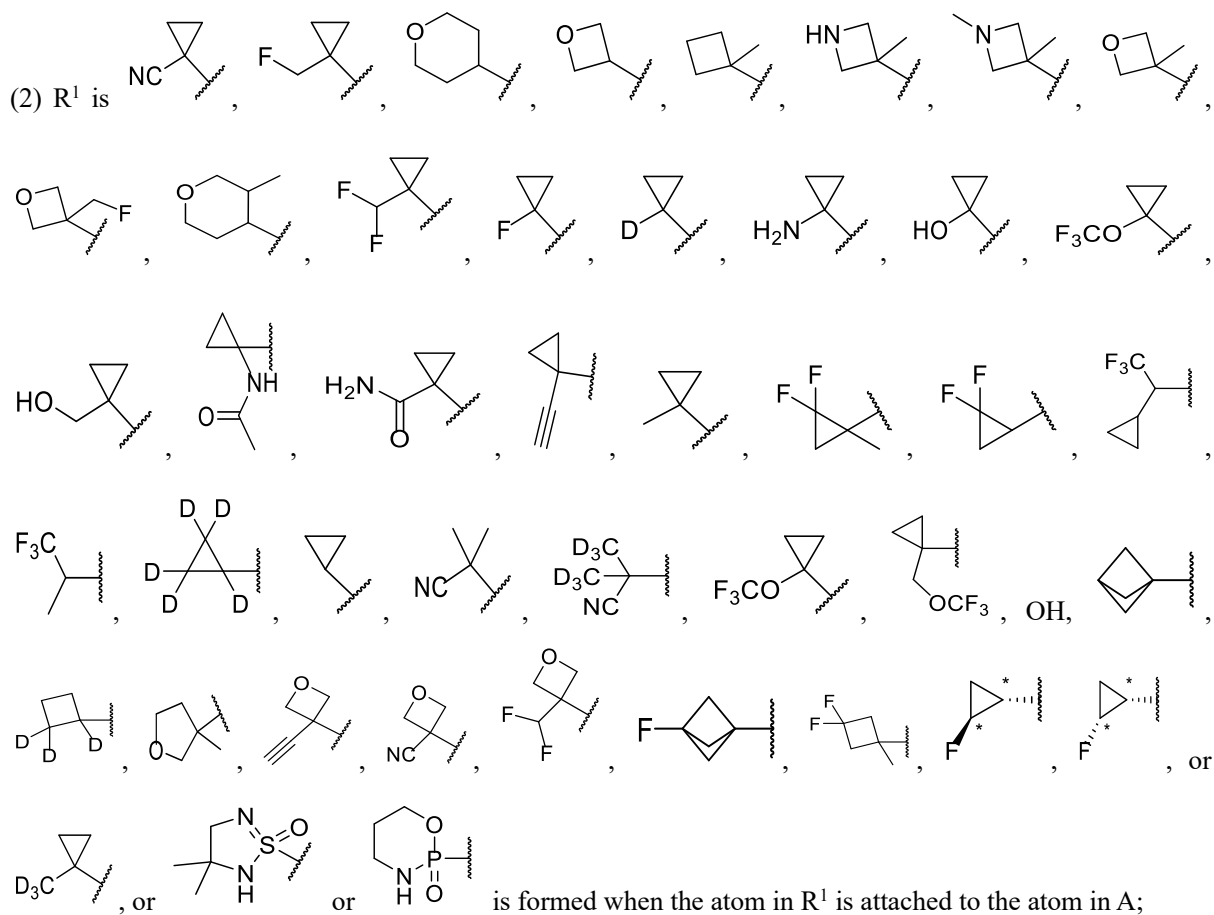
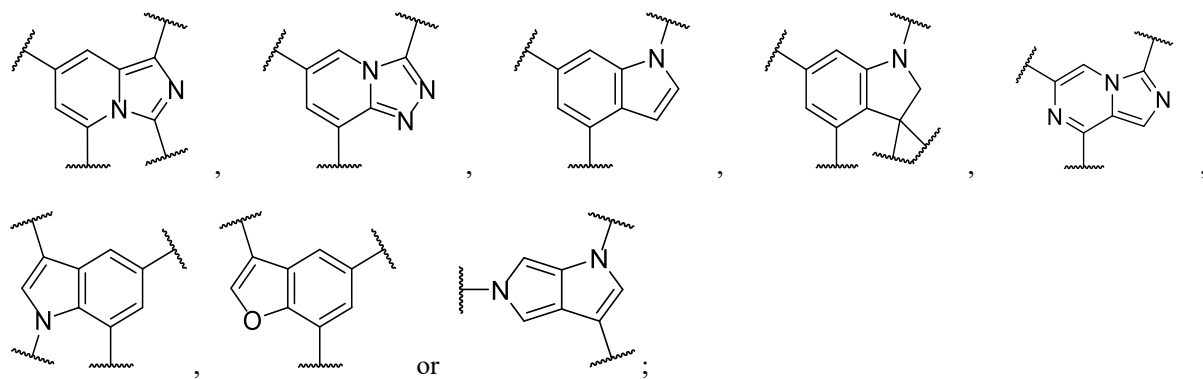


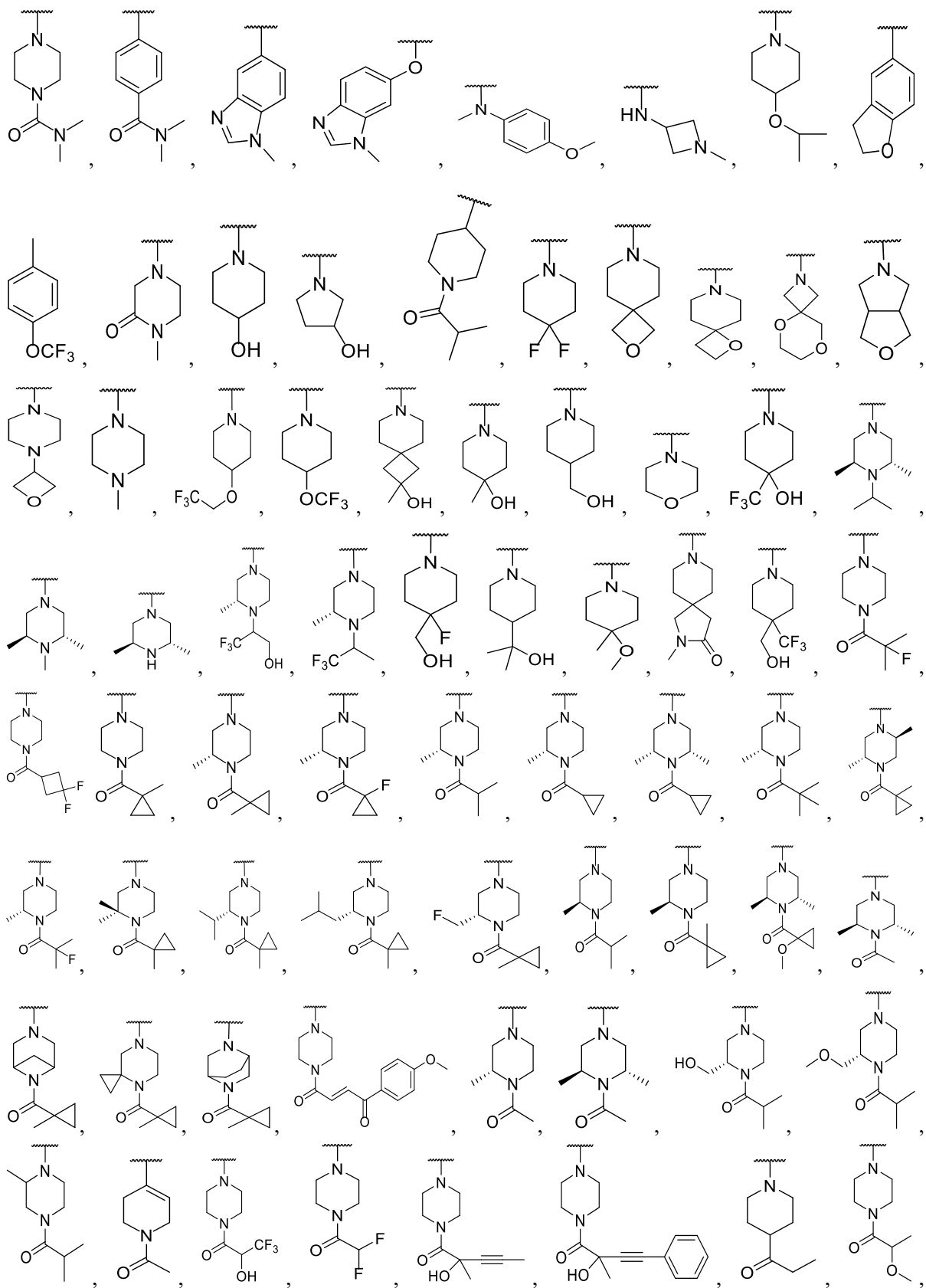
R^G is R^{2-3-2} or $\begin{array}{c} R^{2-3-3} \\ | \\ N \\ | \\ R^{2-3-3} \end{array}$; and

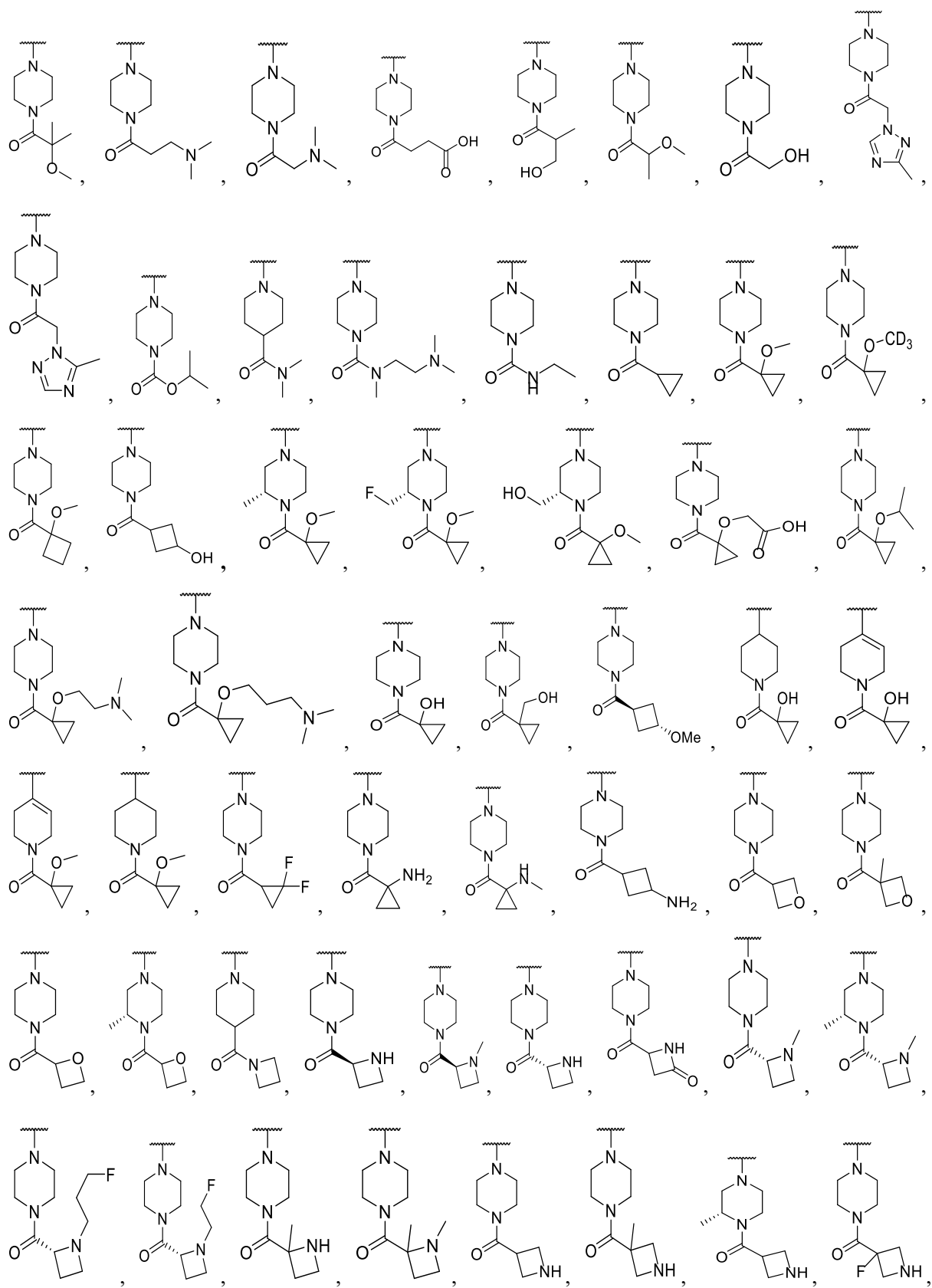
$R^{1-3'}$, R^{1-3} , R^{2-3} , $R^{3-1'}$, R^{2-3-2} , R^{2-3-3} , V^1 , V^2 , n, m, i and j are defined as in claim 17.

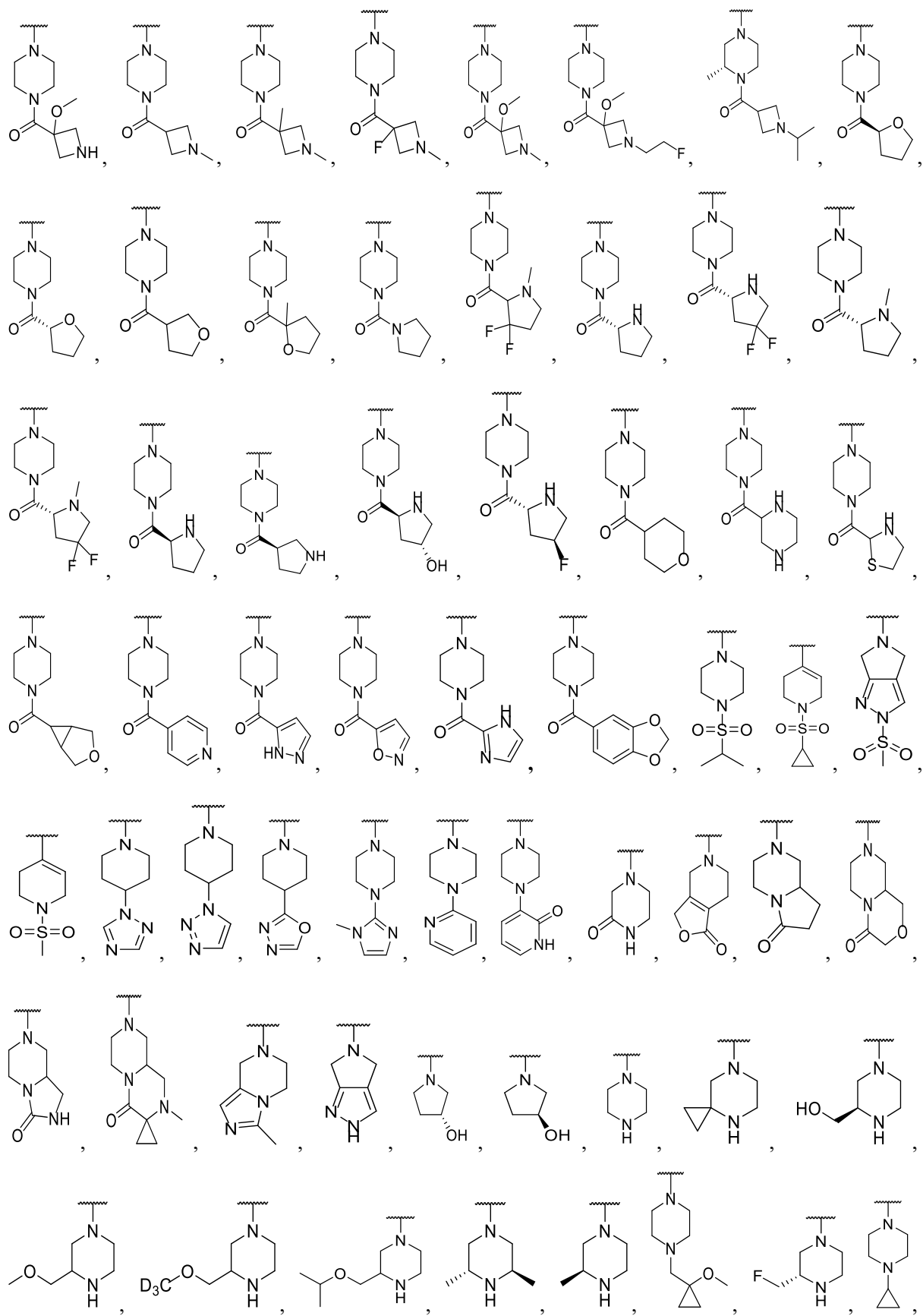
19. The compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to claim 1, wherein the compound of formula I satisfies one or more of the following conditions:

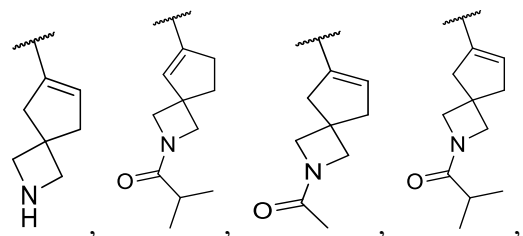
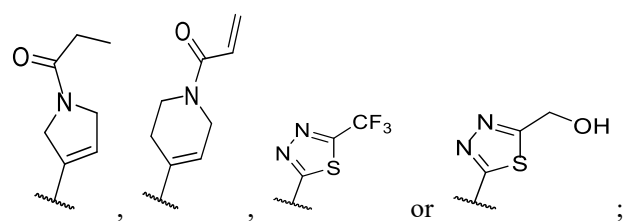
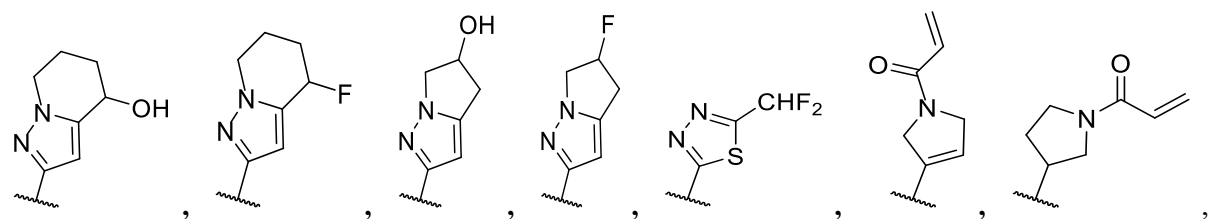
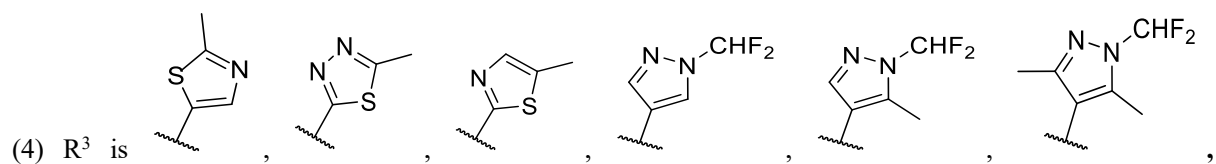
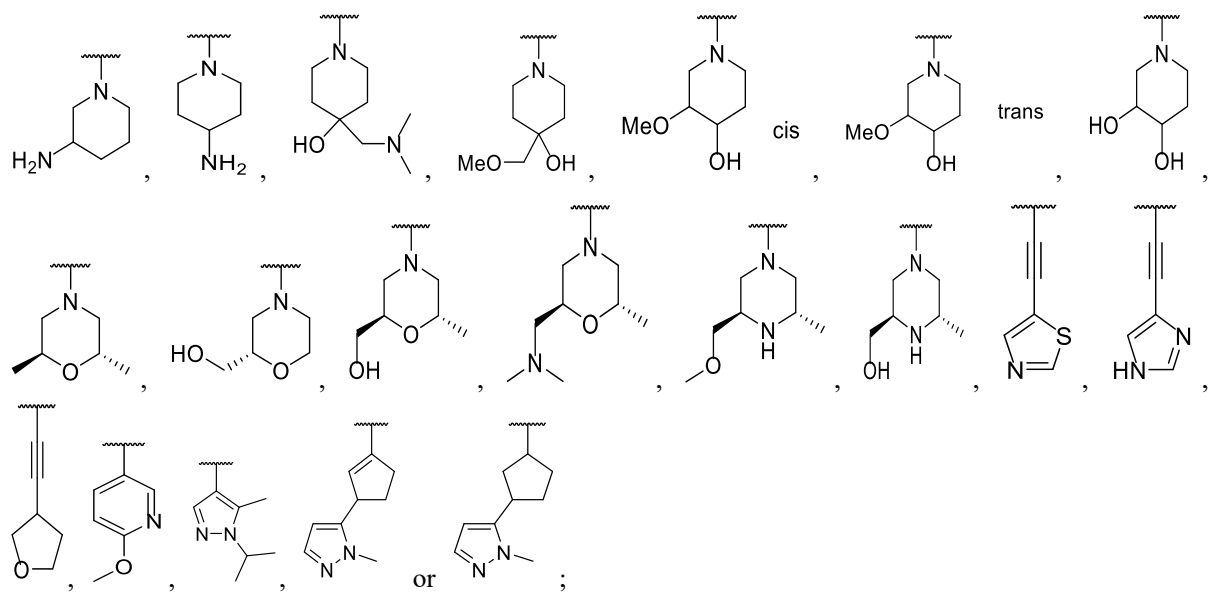




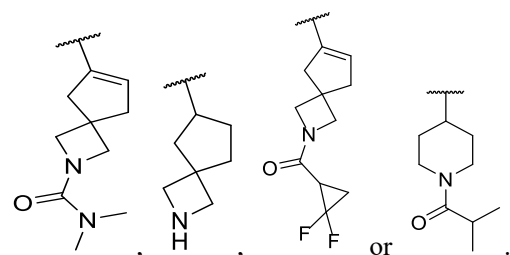




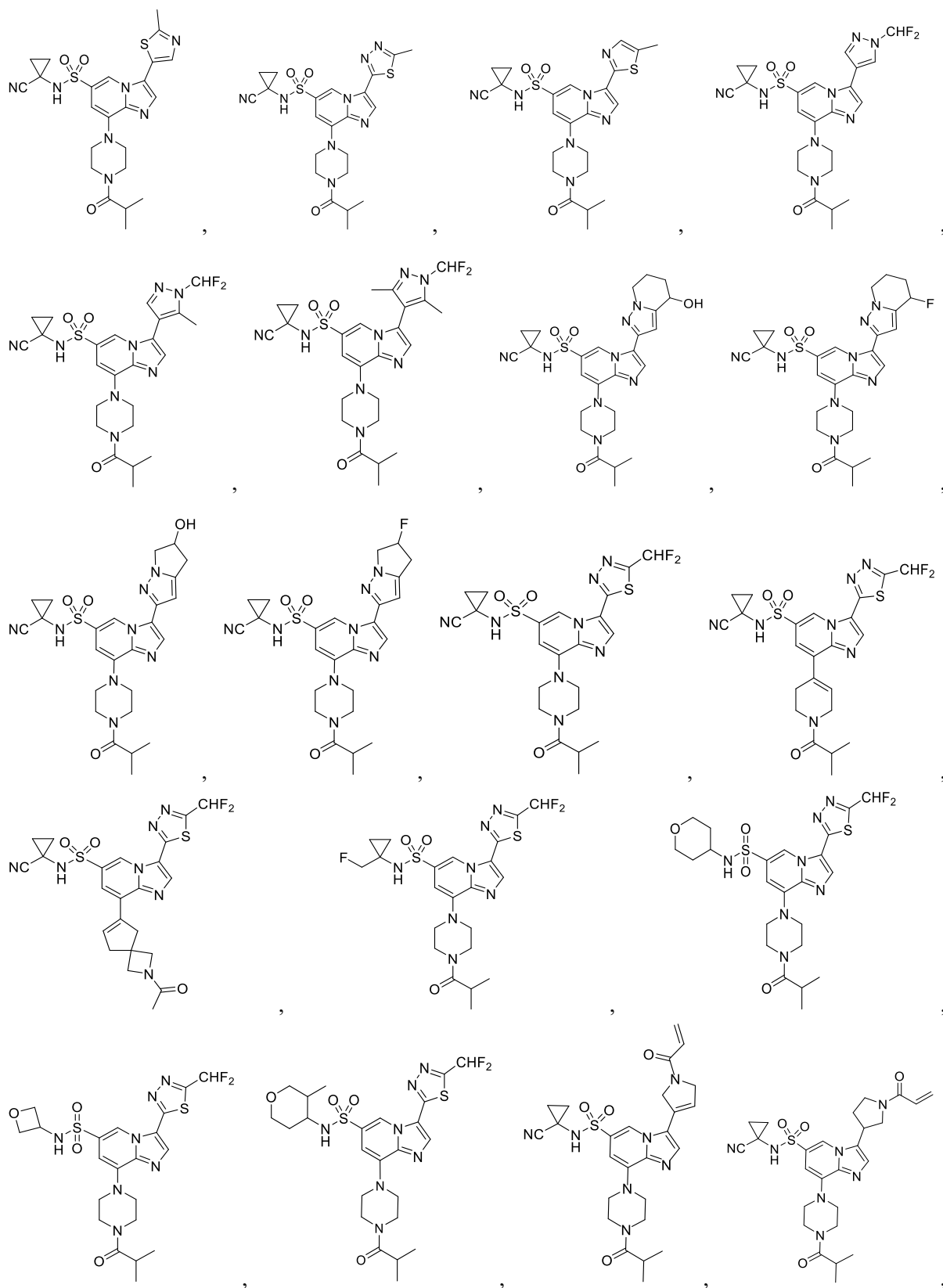


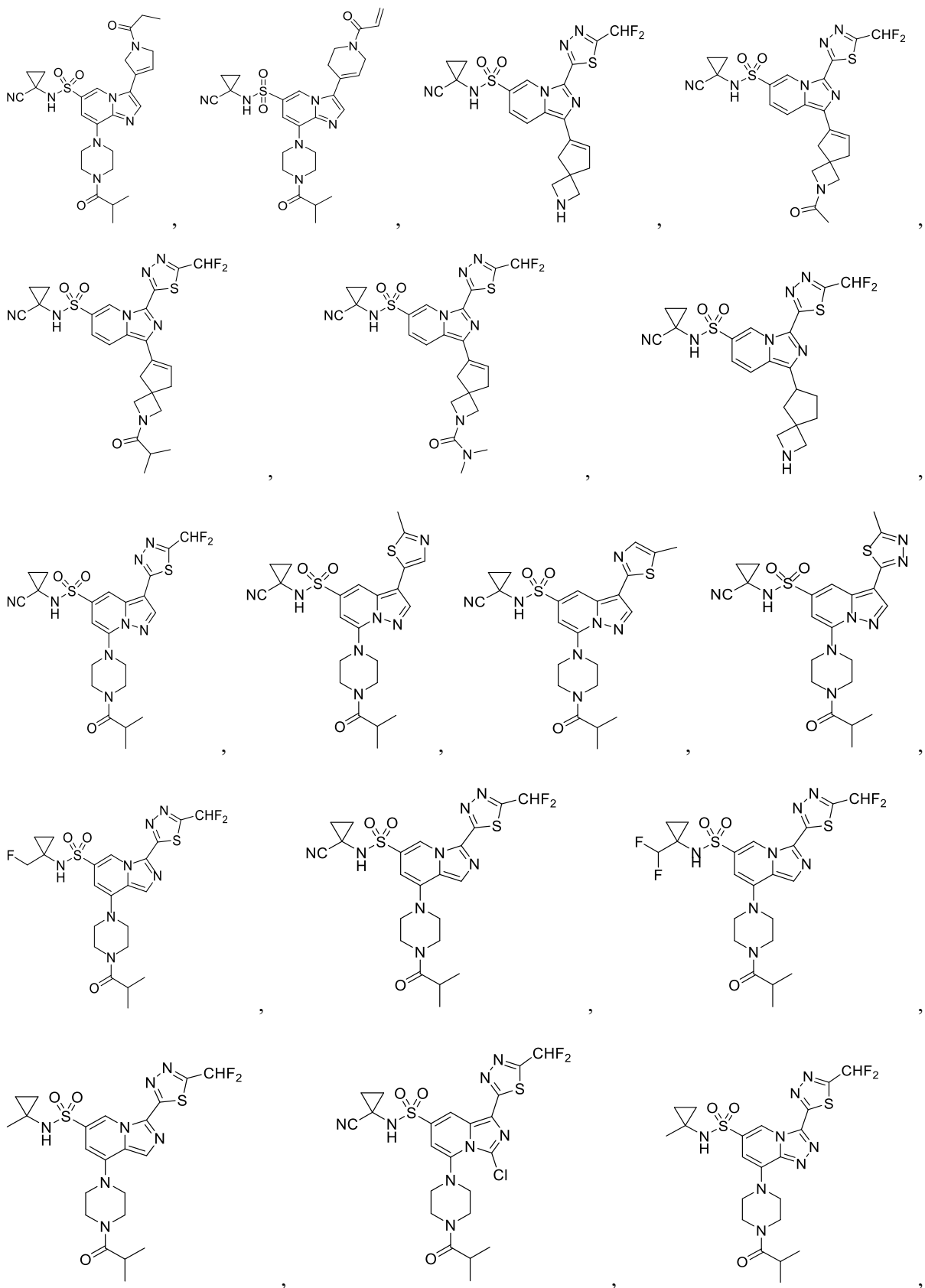


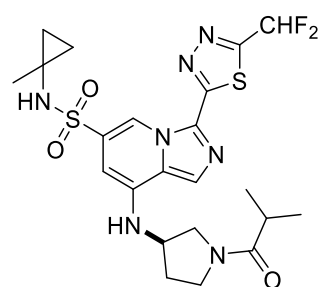
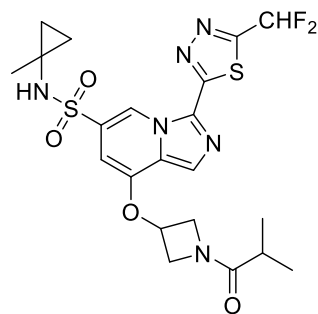
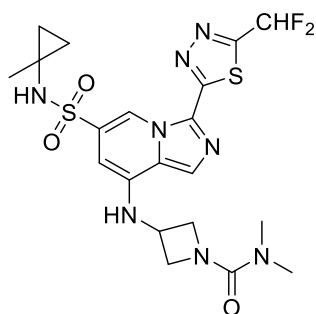
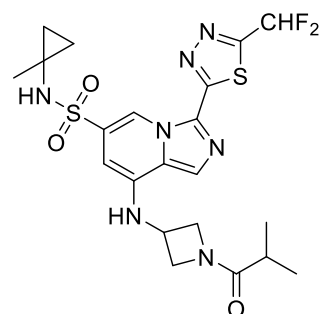
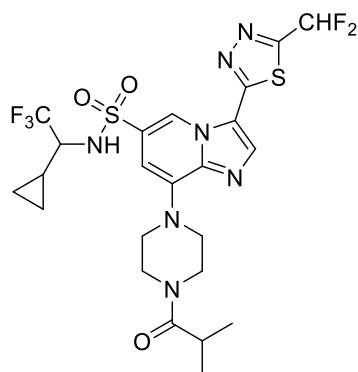
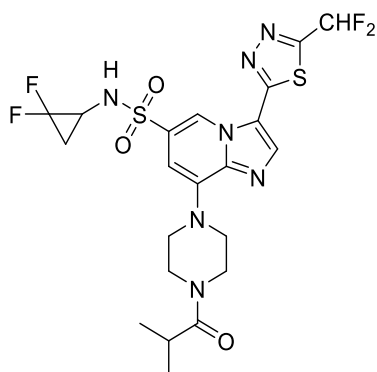
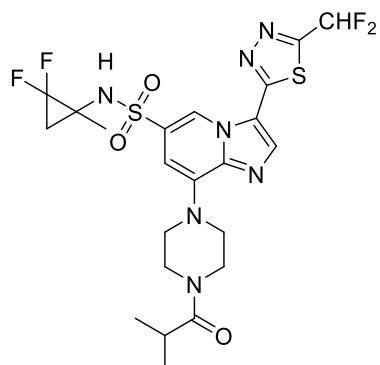
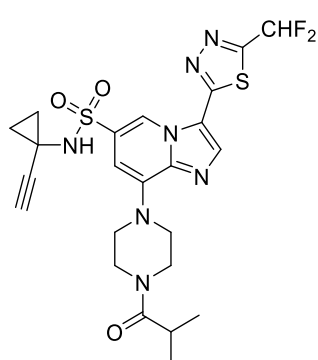
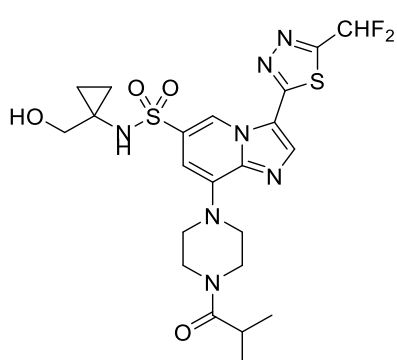
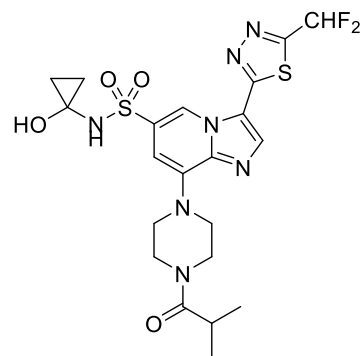
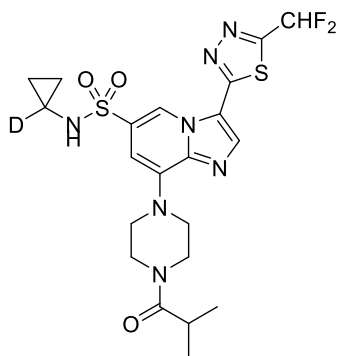
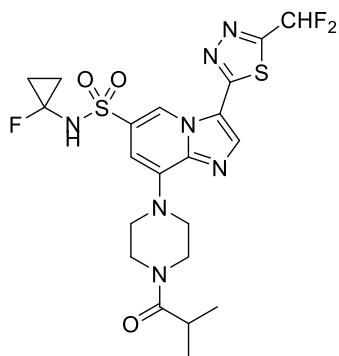
and (5) R^4 is hydrogen, deuterium, Cl, F, CN, methyl,

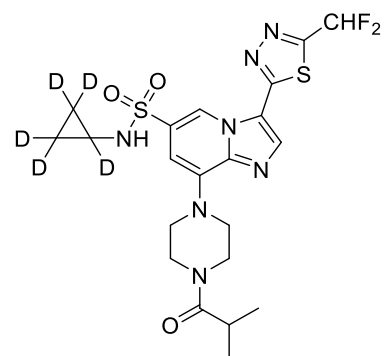
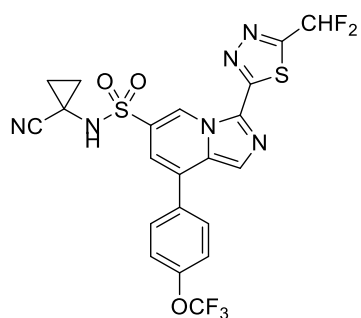
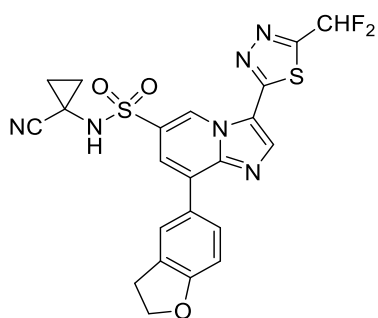
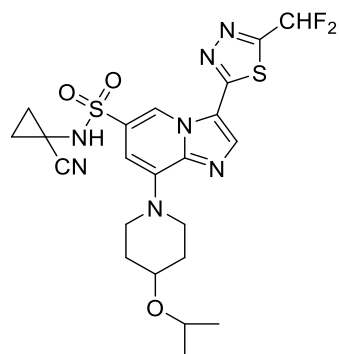
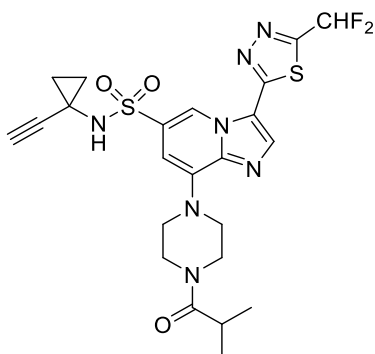
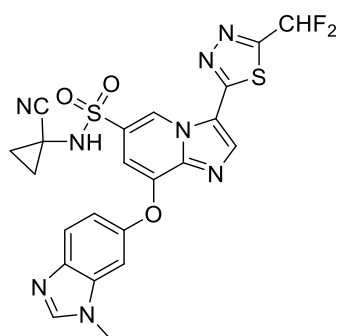
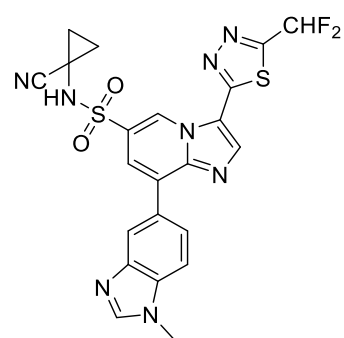
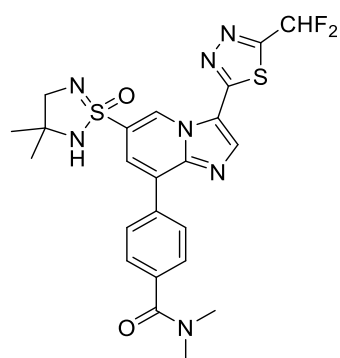
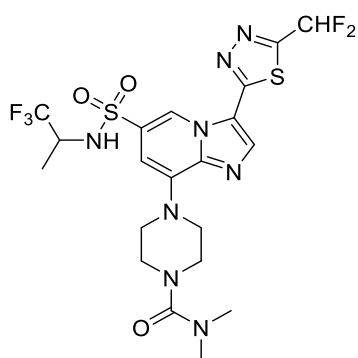
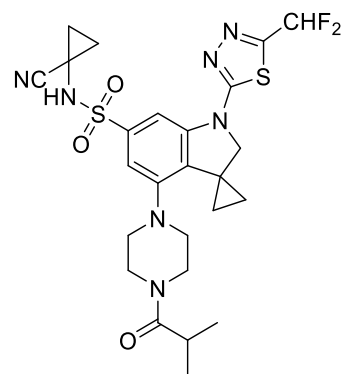
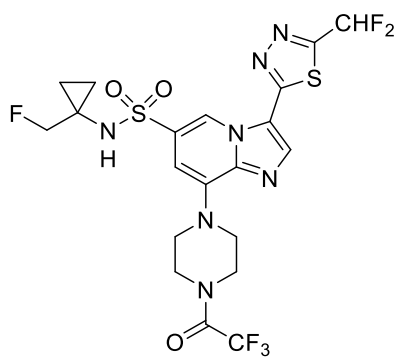
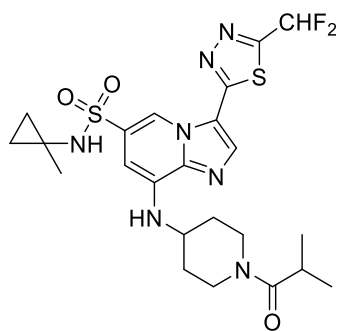


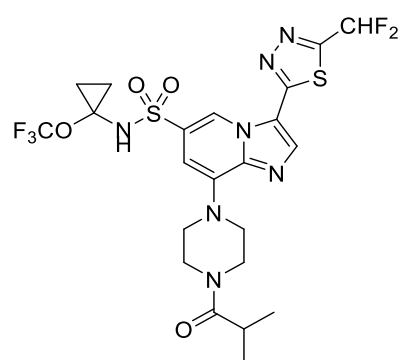
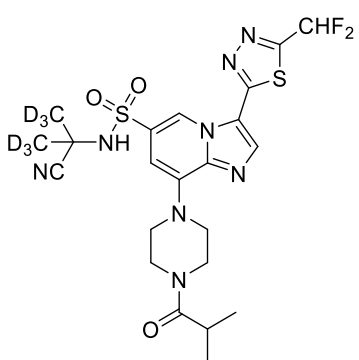
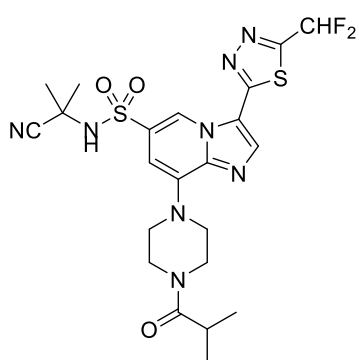
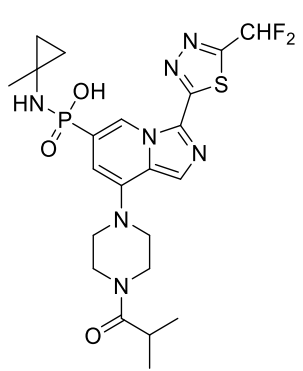
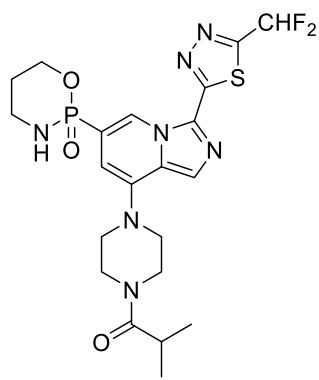
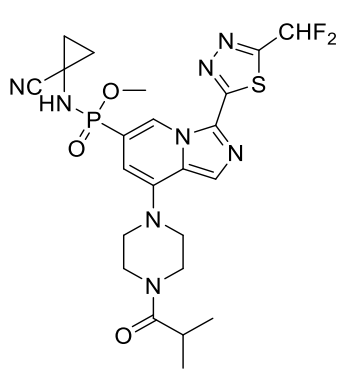
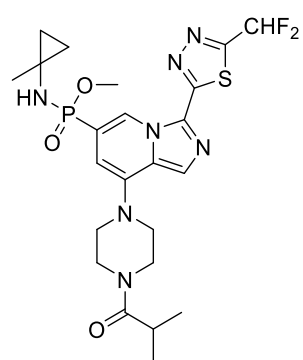
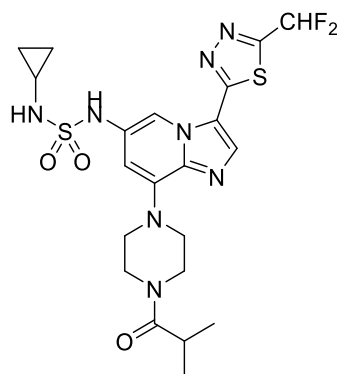
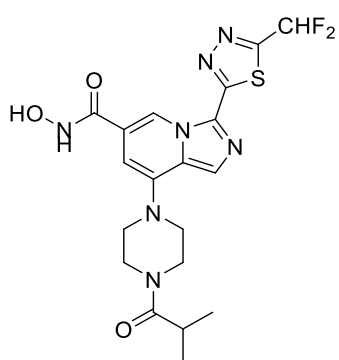
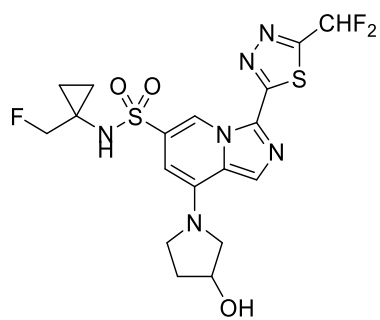
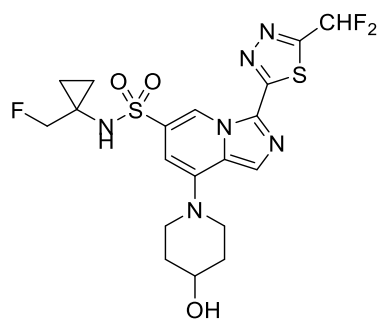
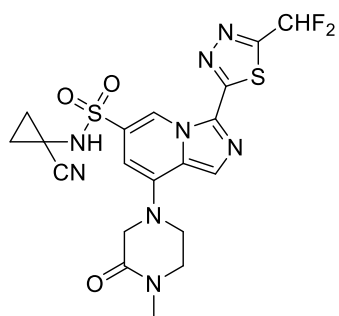
20. The compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to claim 1, wherein the compound of formula I is any one of the following compounds:

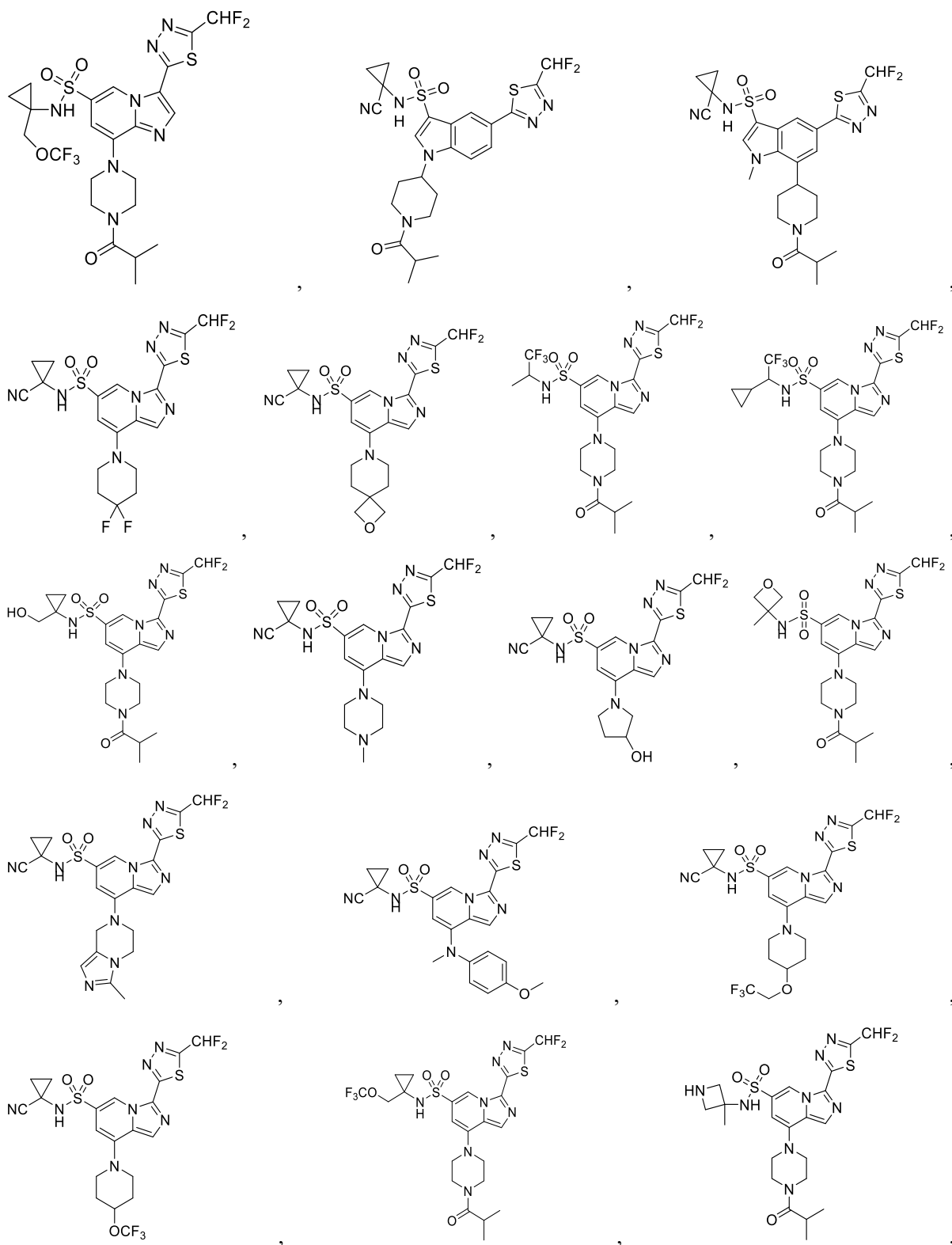


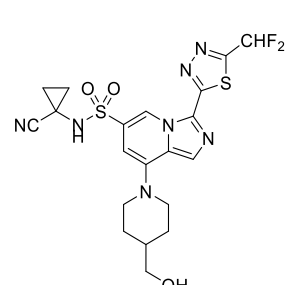
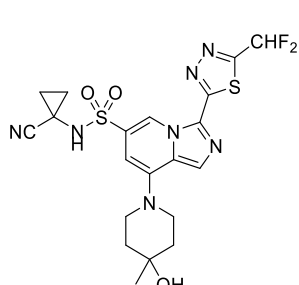
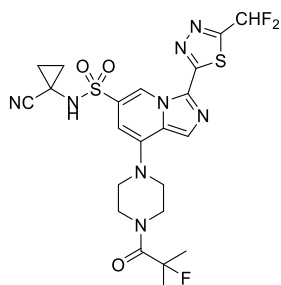
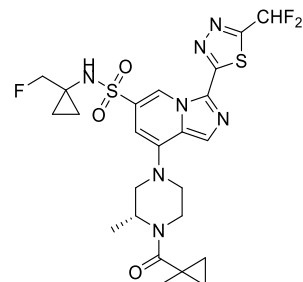
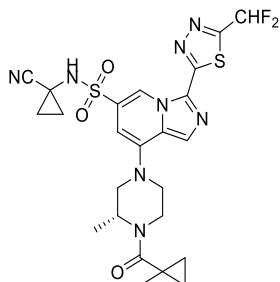
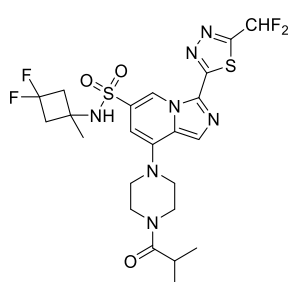
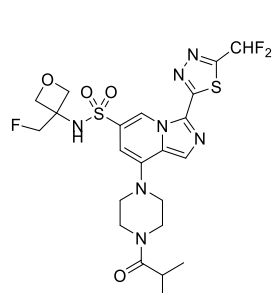
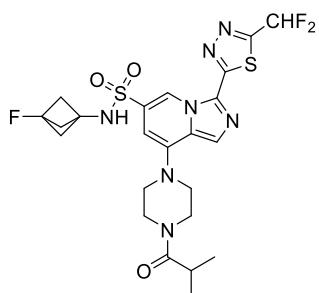
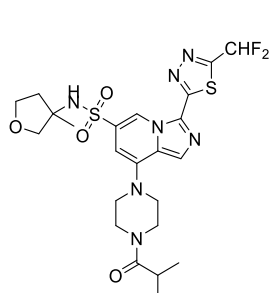
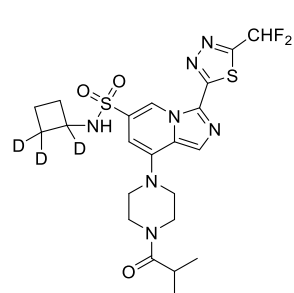
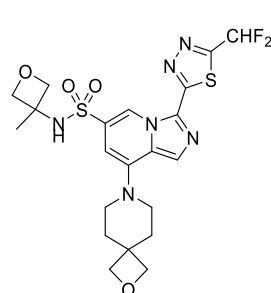
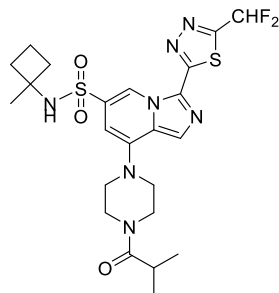
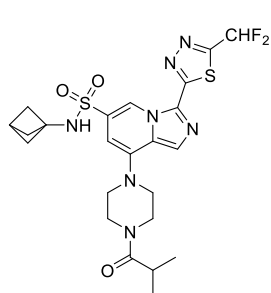
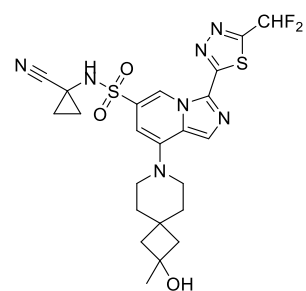
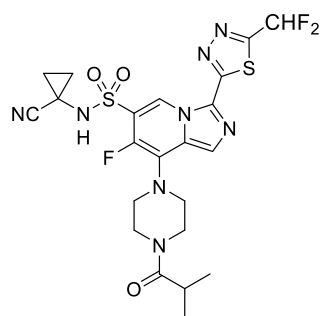
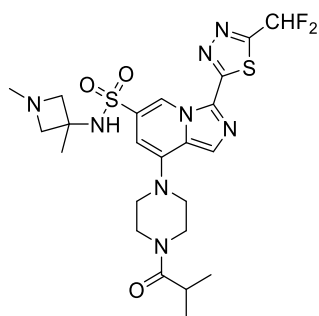




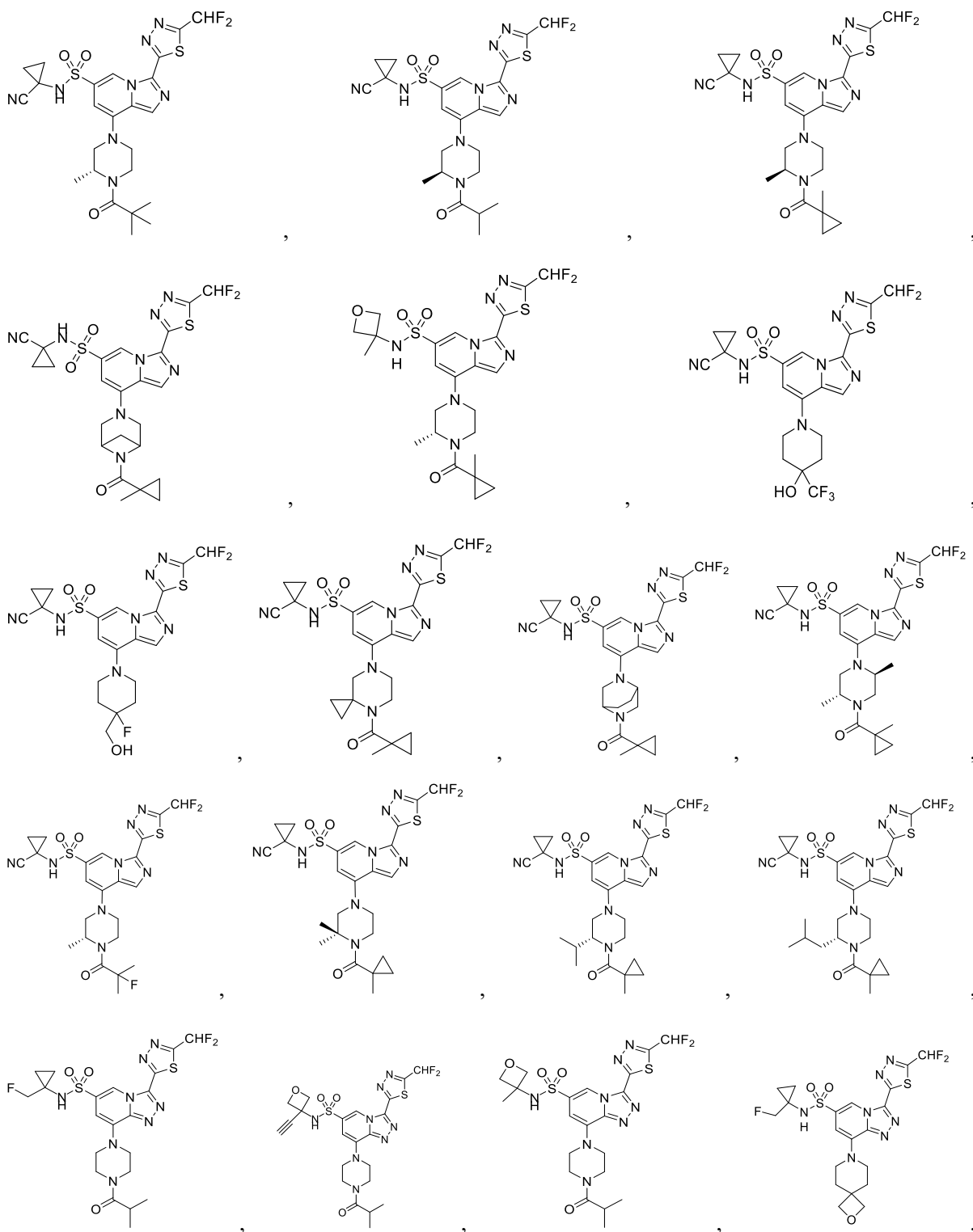


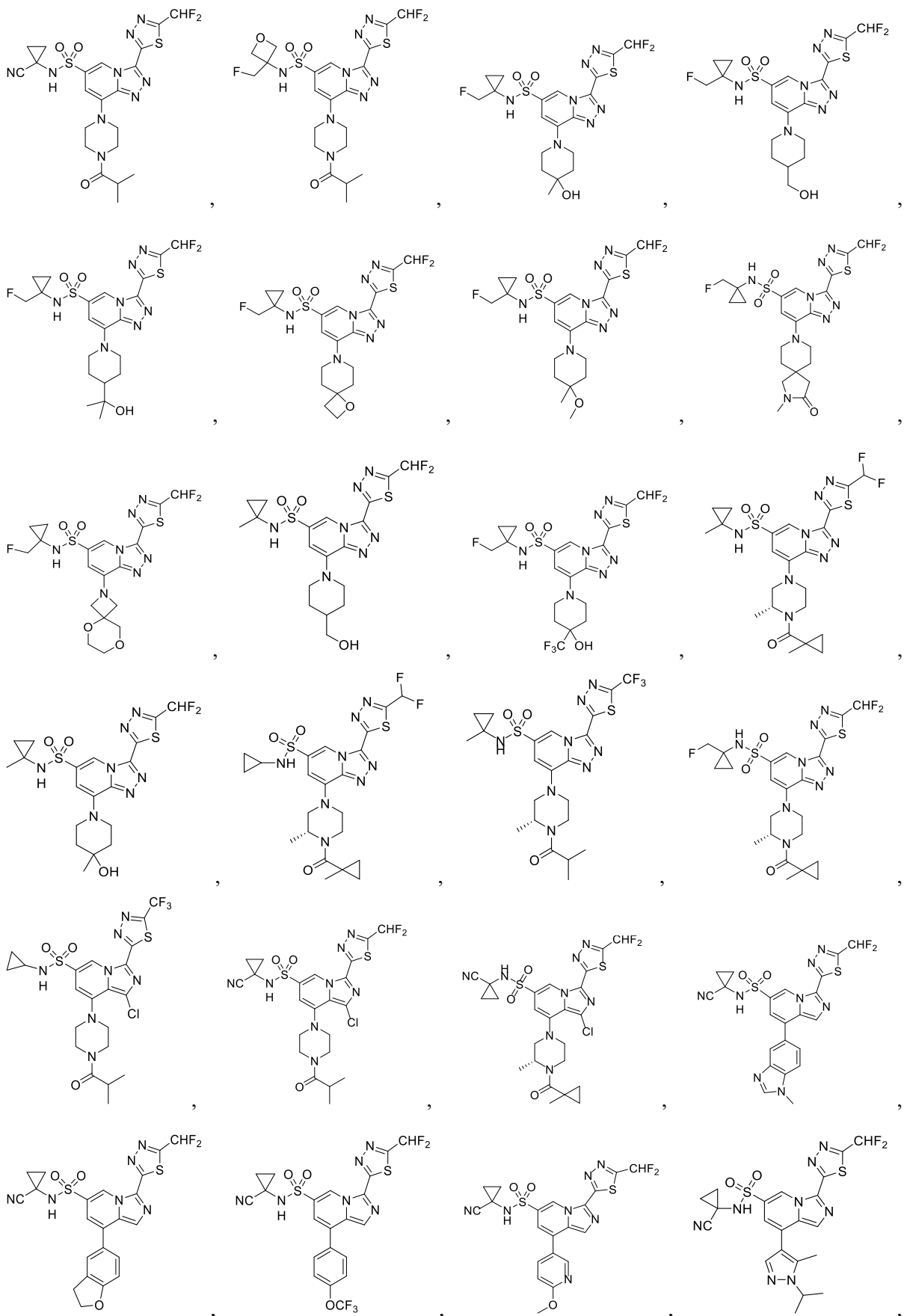


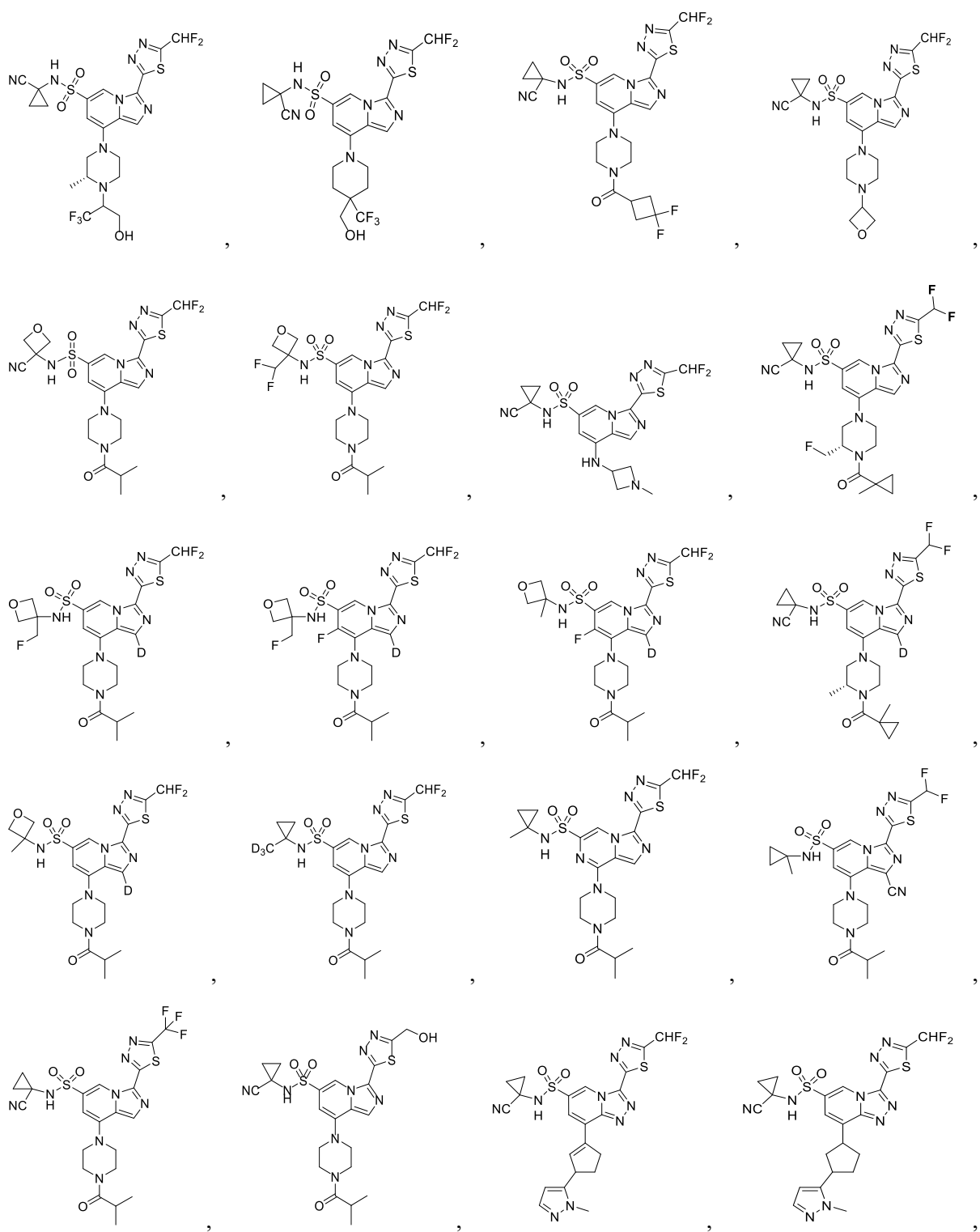


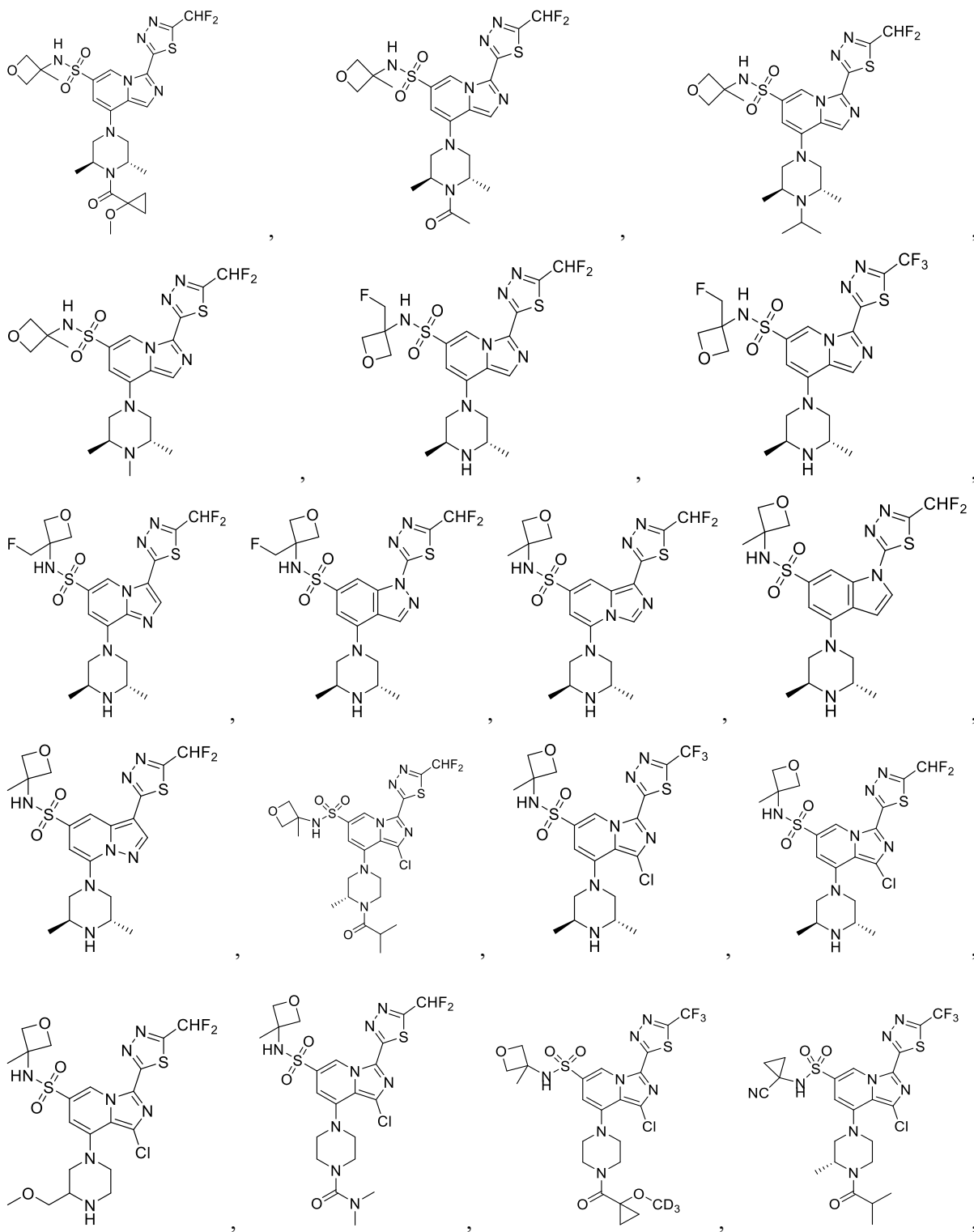


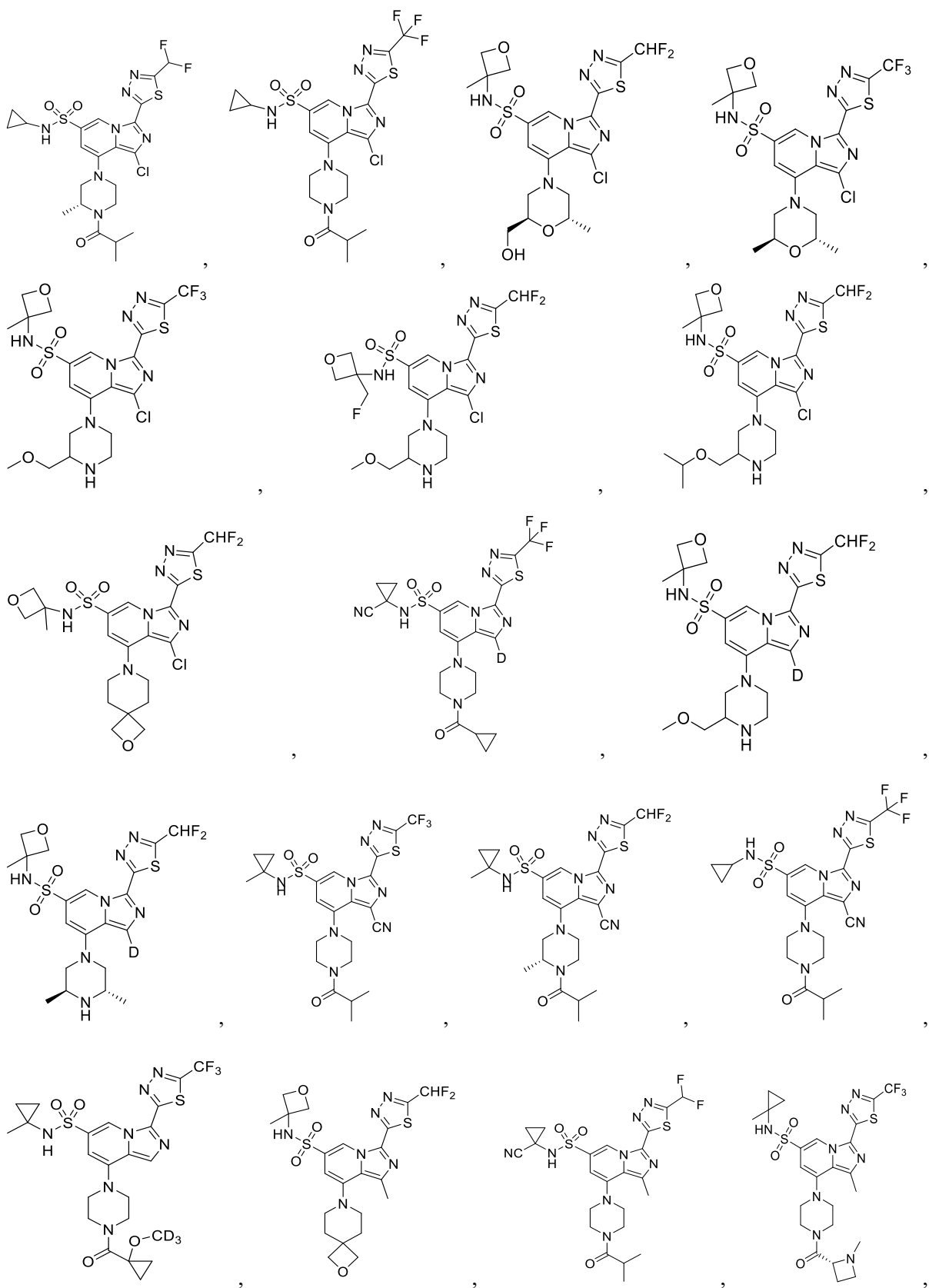


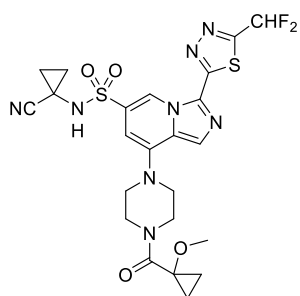




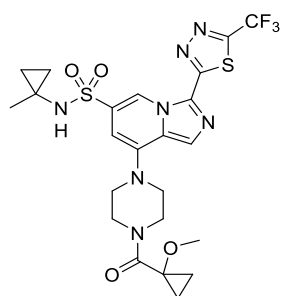




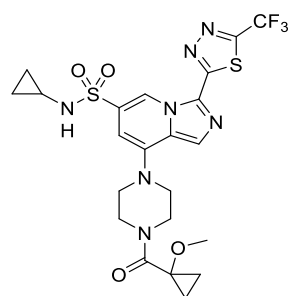




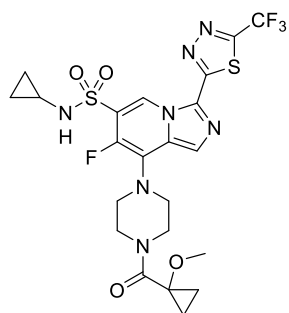
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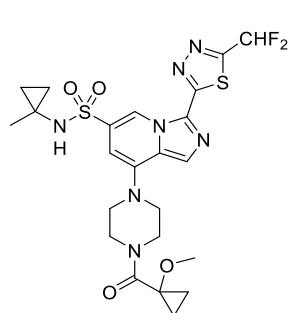
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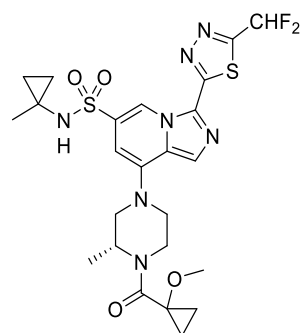
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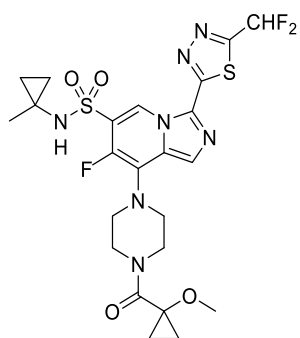
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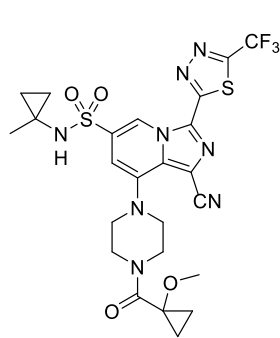
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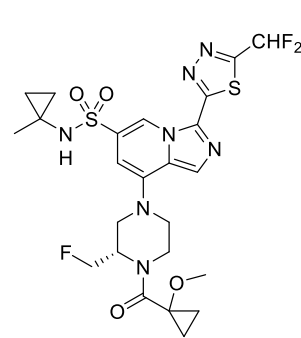
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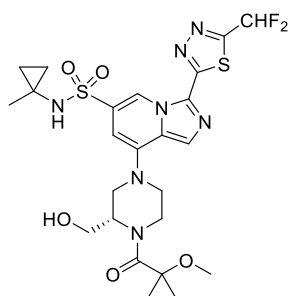
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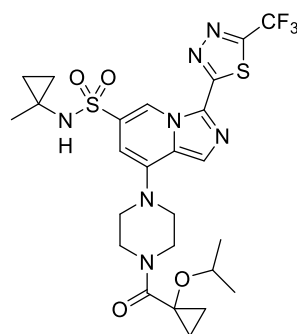
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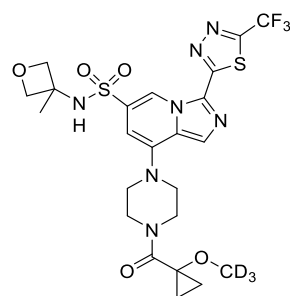
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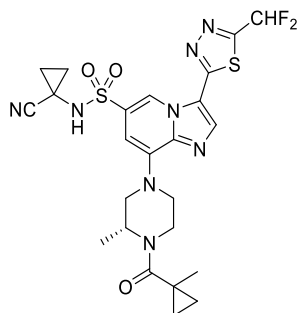
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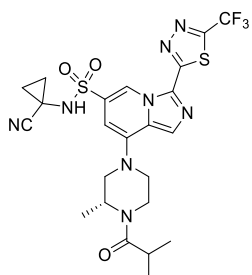
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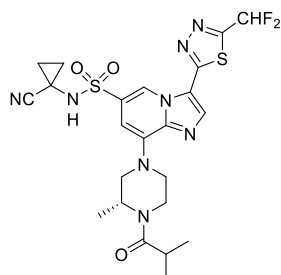
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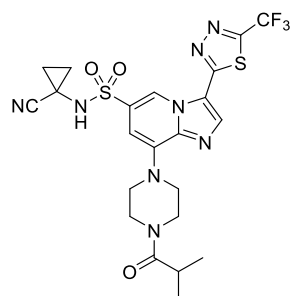
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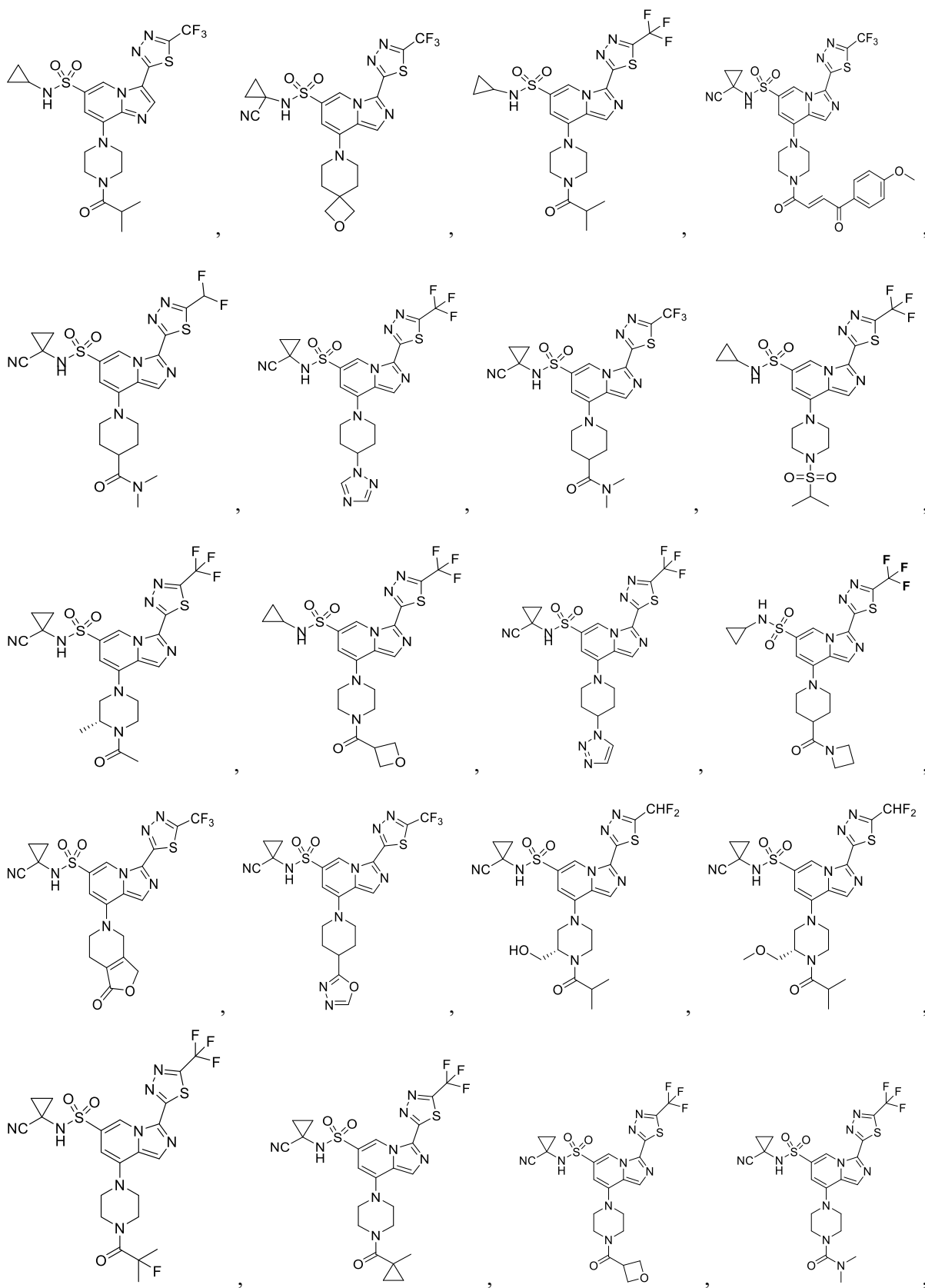
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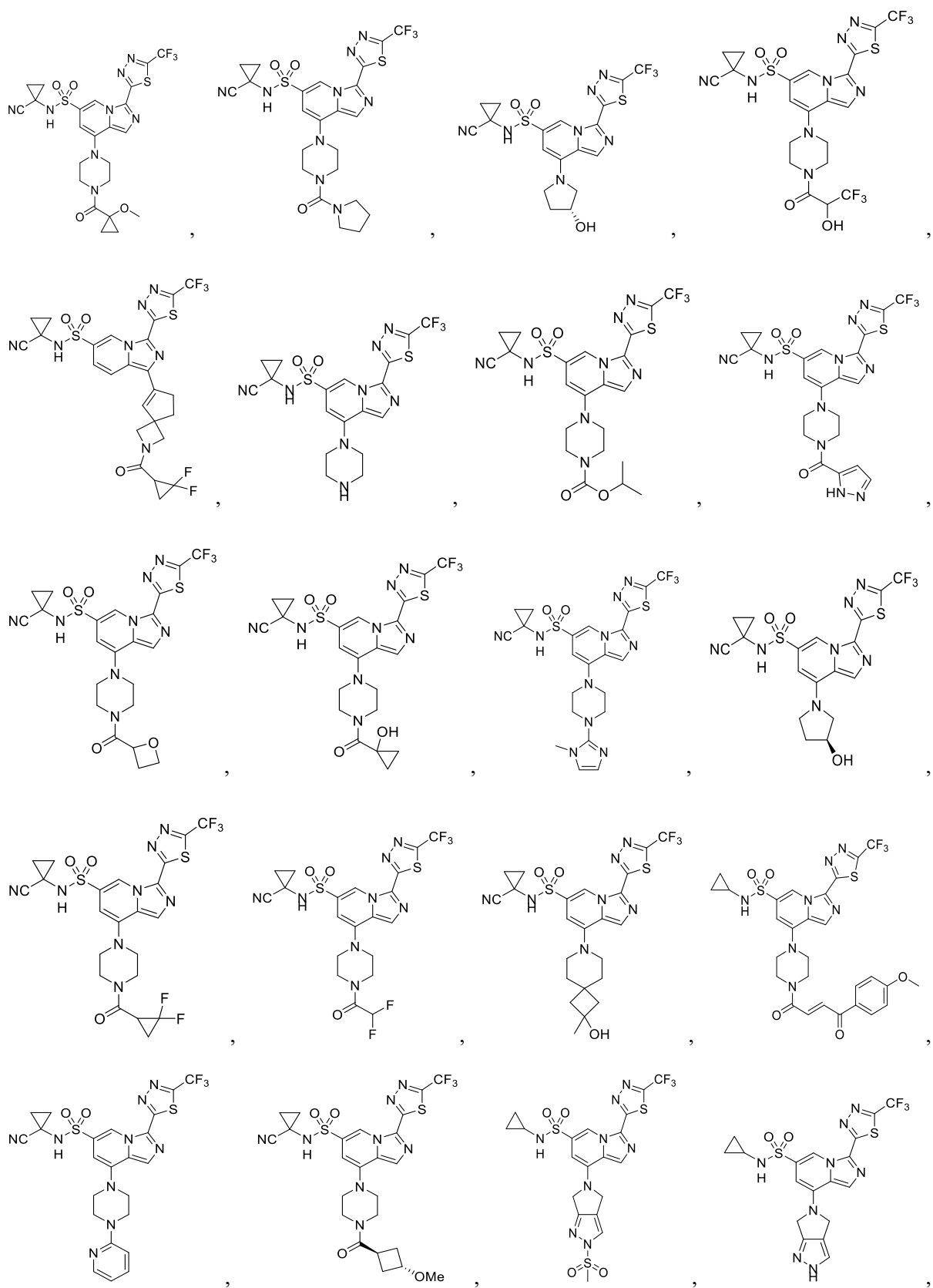


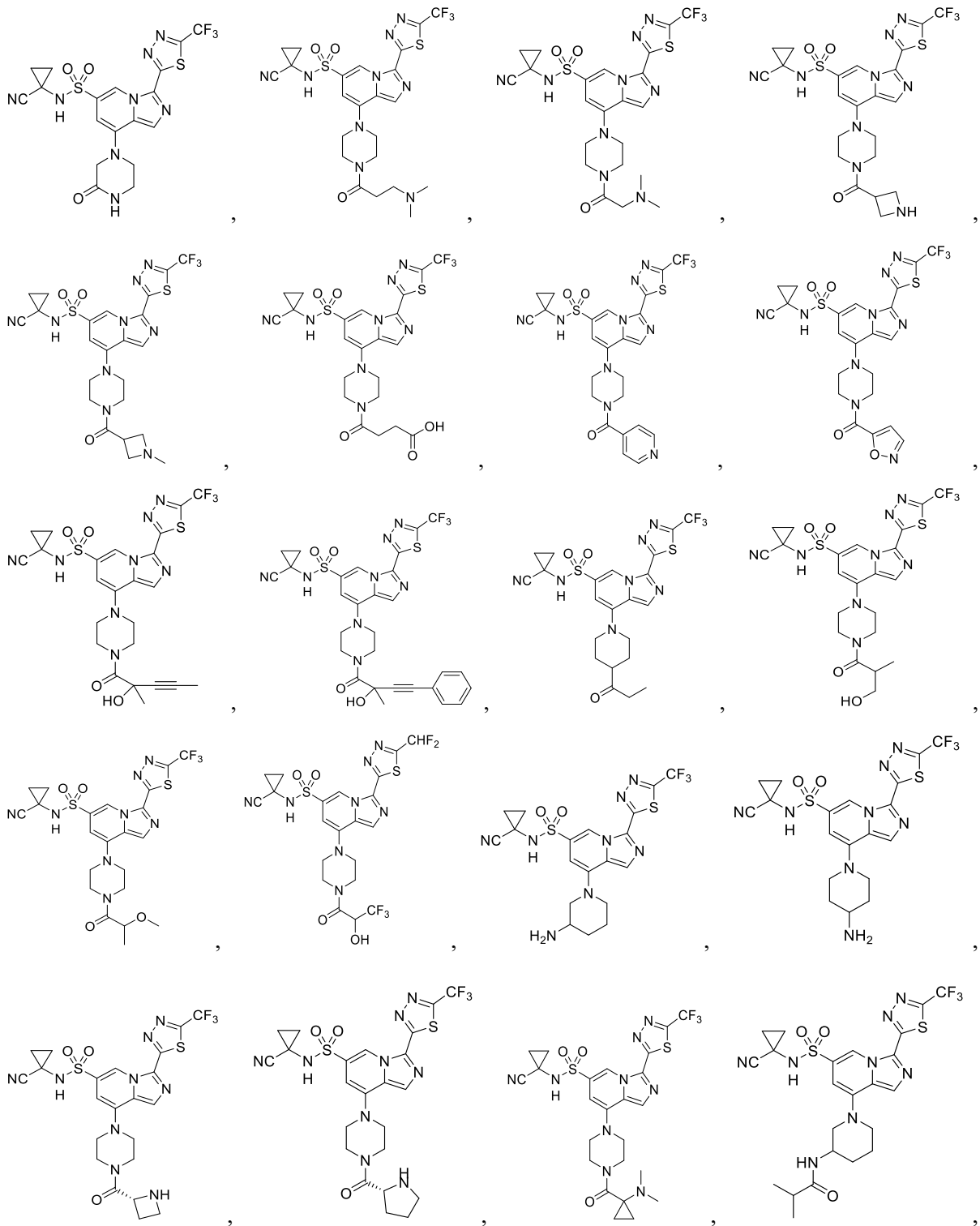
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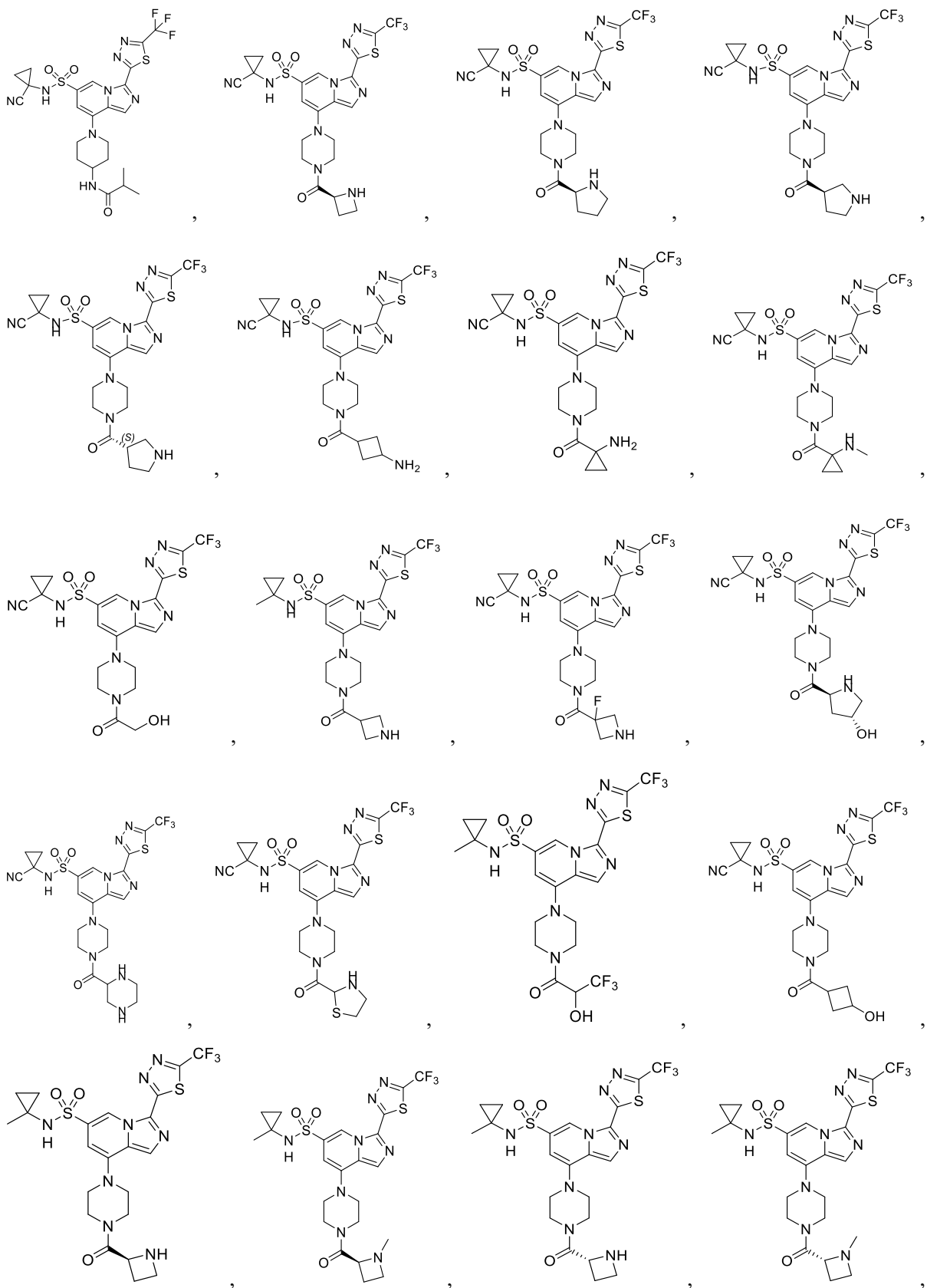


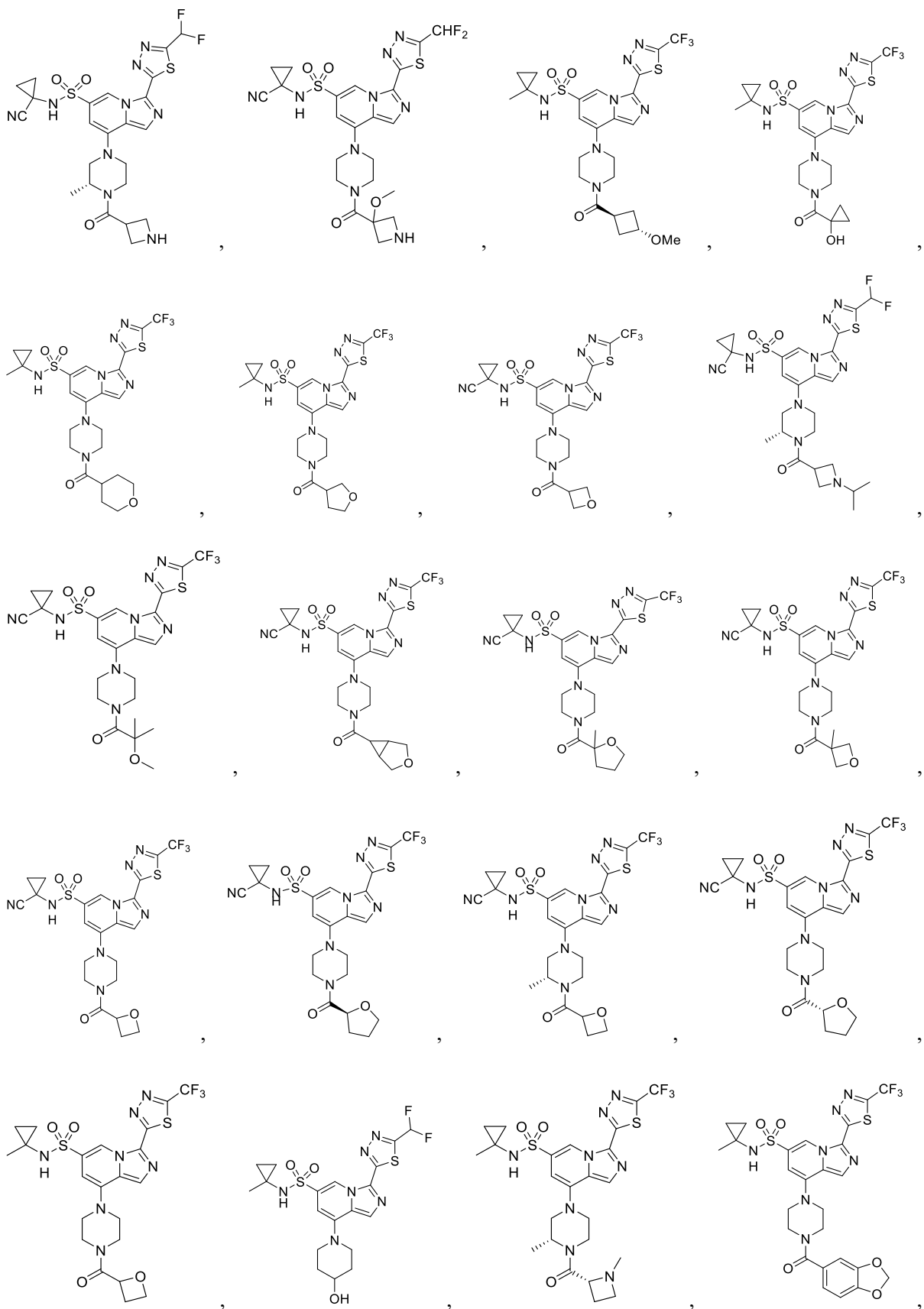
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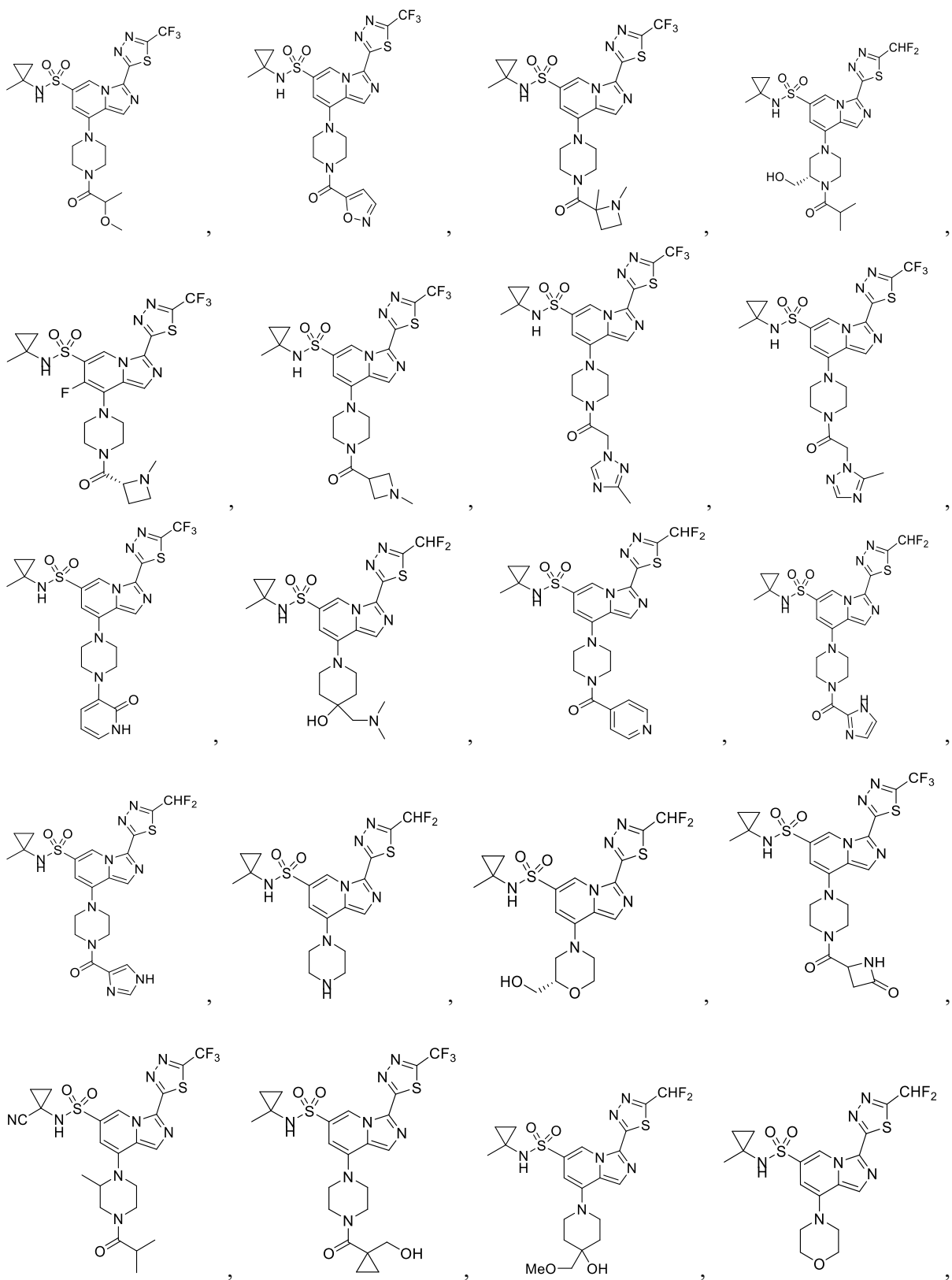


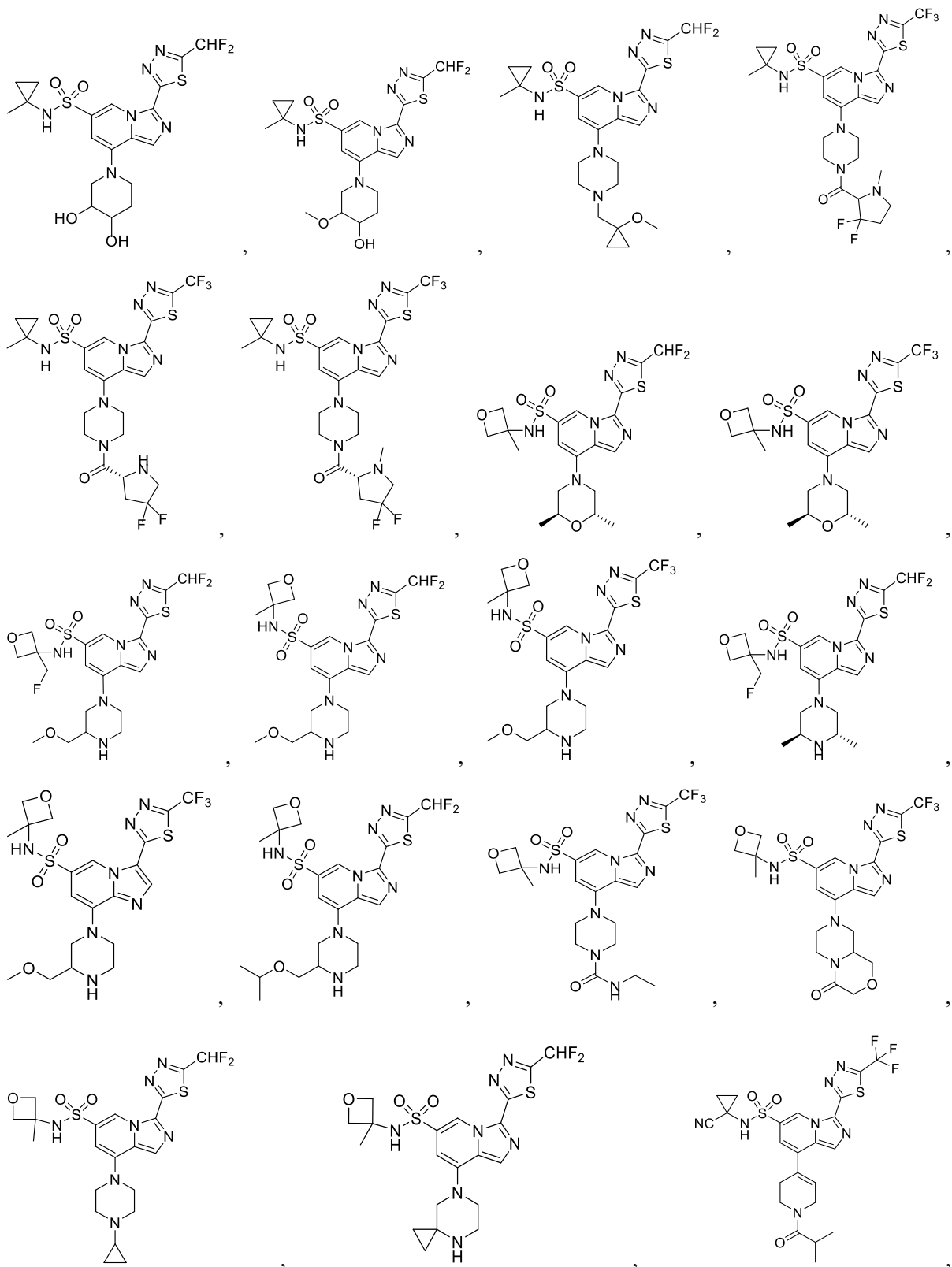


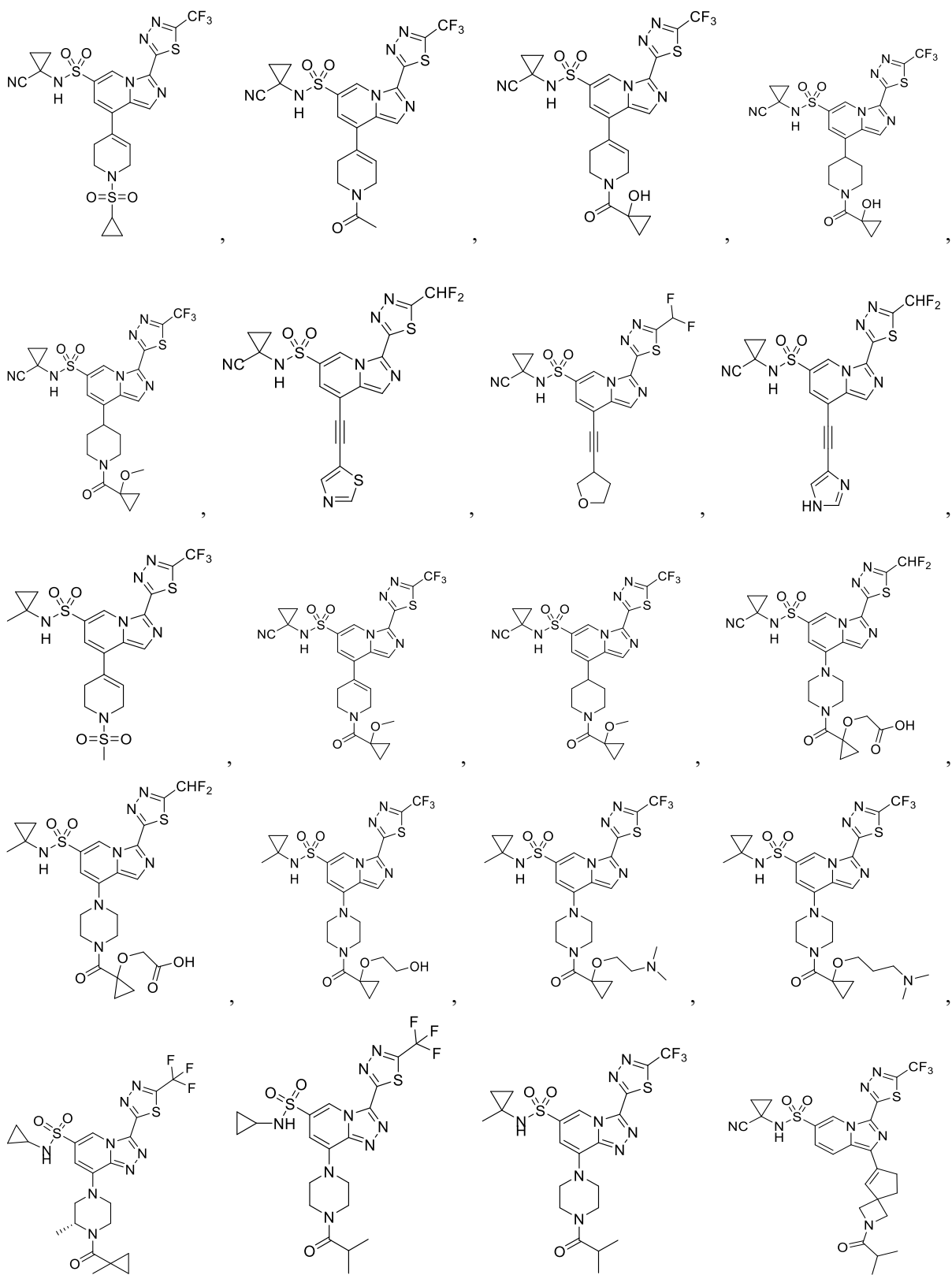


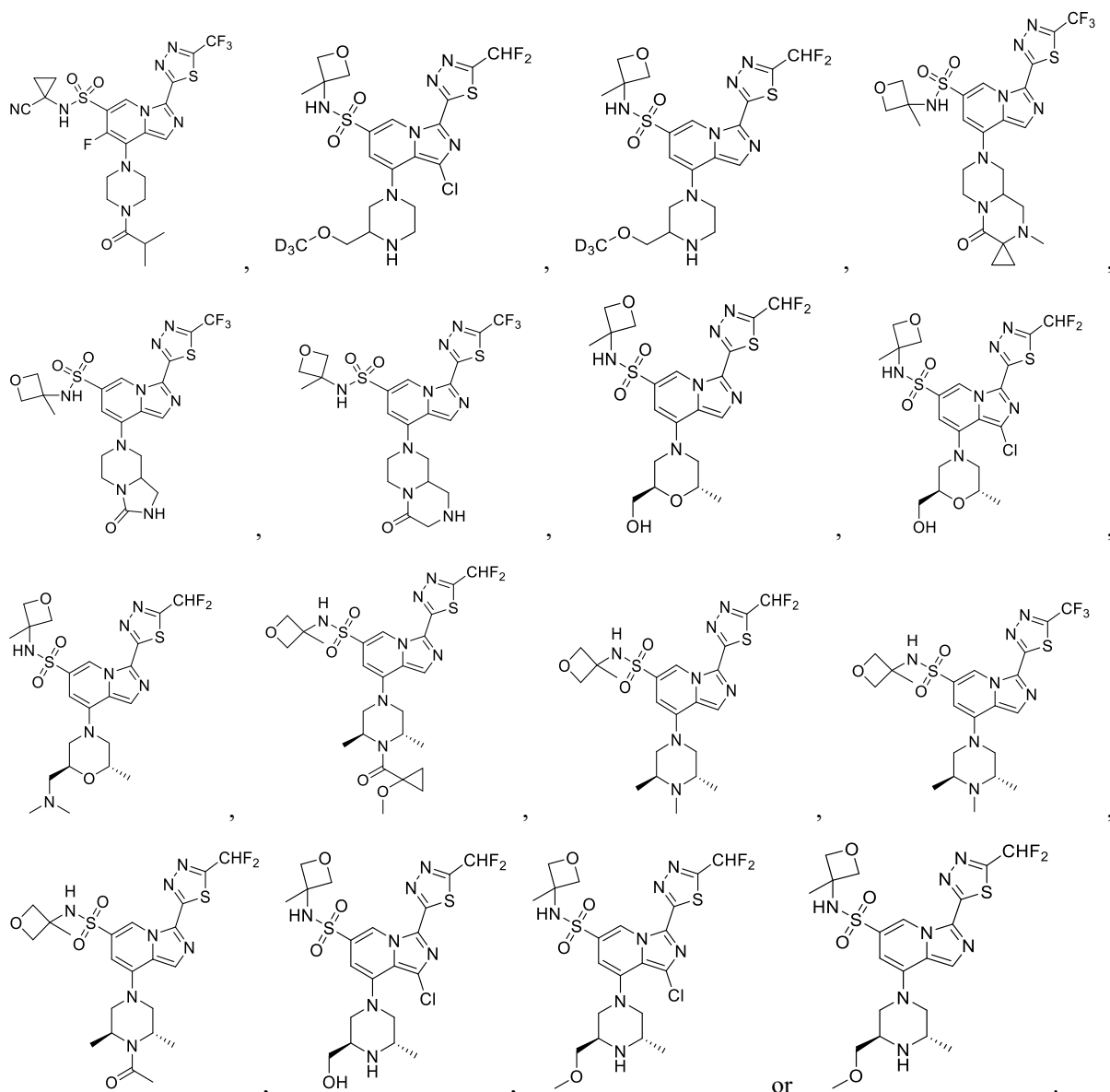










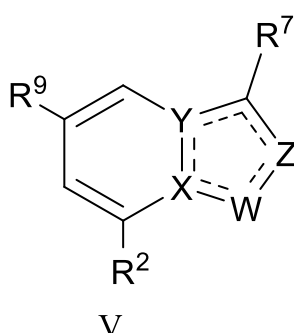
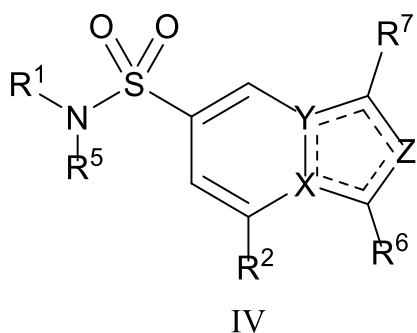
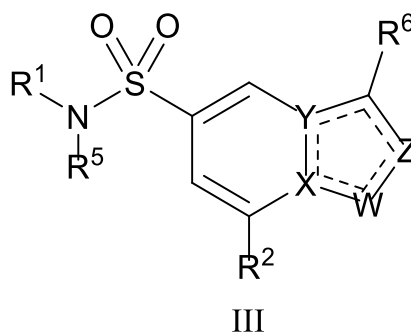


21. A pharmaceutical composition, comprising a substance Z and a pharmaceutic excipient, wherein said substance Z is the compound of formula I, the pharmaceutical composition thereof, or the isotopic compound thereof according to any one of claims 1-20.

22. Use of a substance Z in preparation of a PARG inhibitor and a medicament for treating and/or preventing PARG-related diseases, wherein said substance Z is a compound of formula I, a pharmaceutically acceptable salt thereof or an isotopic compound thereof; and the PARG-related diseases can be breast cancer, for example, triple negative breast cancer.

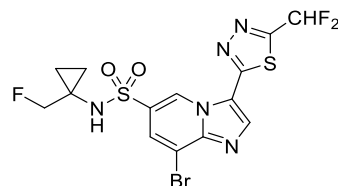
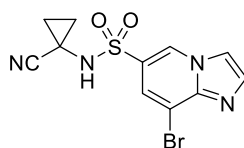
23. Use of a substance Z in preparation of a medicament for treating and/or preventing breast cancer, wherein said substance Z is the compound of formula I, the pharmaceutically acceptable salt thereof or the isotopic compound thereof according to any one of claims 1-20, and said breast cancer can be triple negative breast cancer.

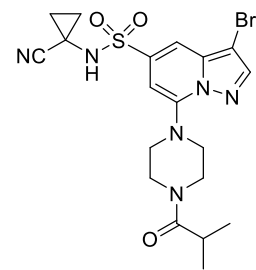
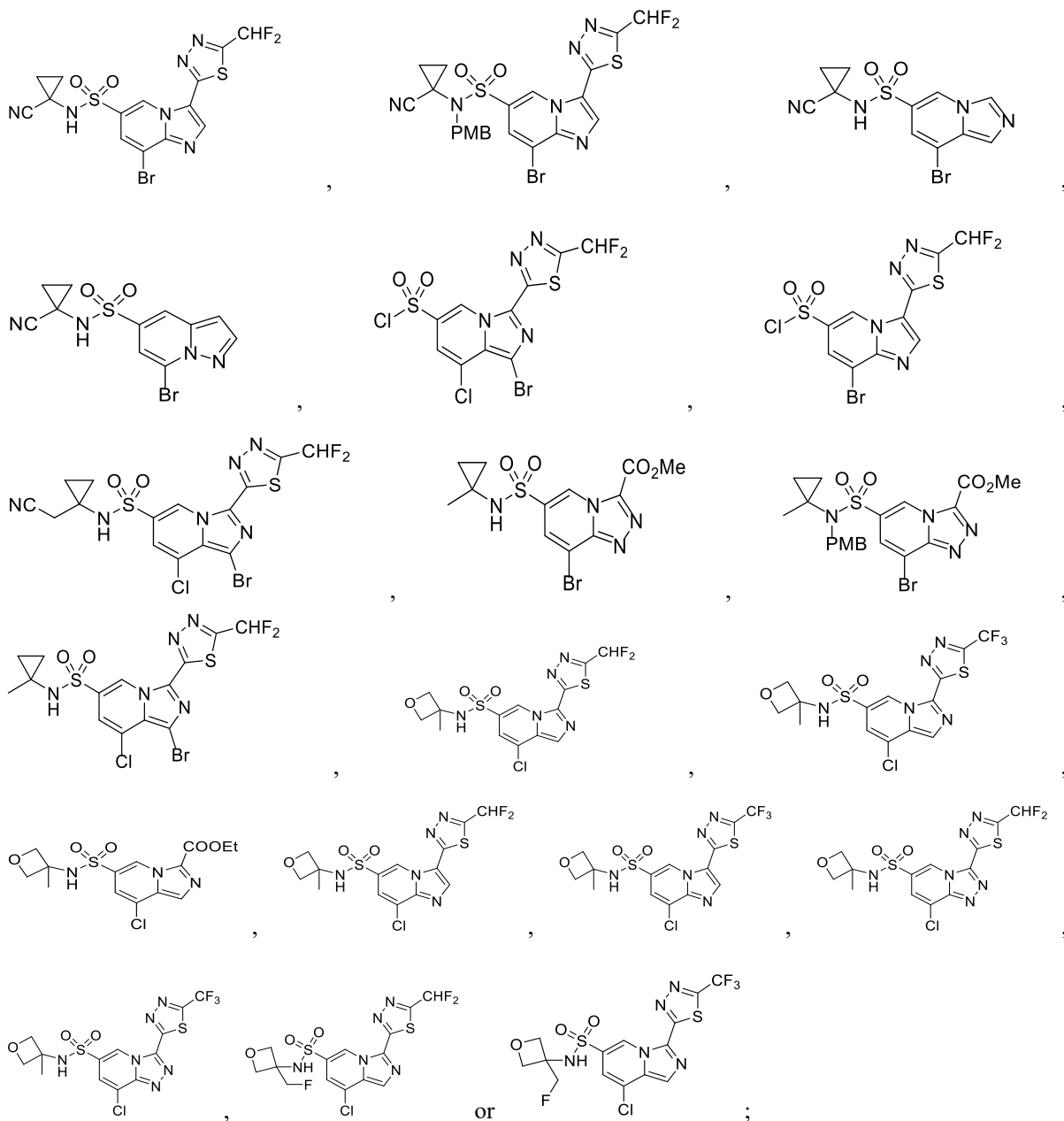
24. The compound of formula II, III, IV or V or a salt thereof,


$$\text{---} \text{C}(=\text{O})\text{O-R}^8$$

The image shows two chemical structures. On the left is a benzyl thiol derivative, represented as a wavy line connected to a sulfur atom (S), which is further connected to a methylene group (-CH₂-) and a benzene ring. On the right is a sulfonyl chloride derivative, represented as a wavy line connected to a sulfur atom (S), which is double-bonded to two oxygen atoms (O) and single-bonded to a chlorine atom (Cl). The sulfur atom is also bonded to an R⁶ group.

and/or, in R⁹, said halogen can be fluorine, chlorine, bromine or iodine, for example, chlorine or bromine.

CC1(C)N(C#N)S(=O)(=O)c2cc(Br)c3nc(C(=O)O)cnc3c2C4=CC=CC=C4N#CC1(C)NCS(=O)(=O)c2cc(Br)c3nc(C(=O)O)cnc3n2



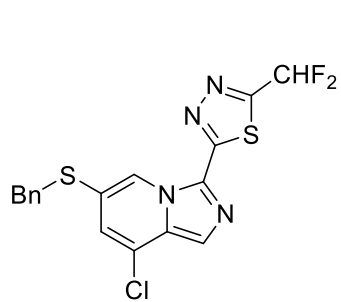
and/or , said compound of formula III is of any one of the following structures:



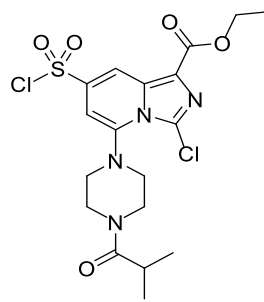
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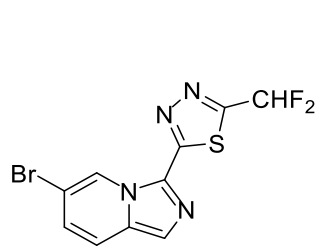
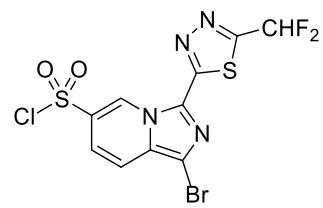
and/or , said compound of formula V is of any one of the following structures:



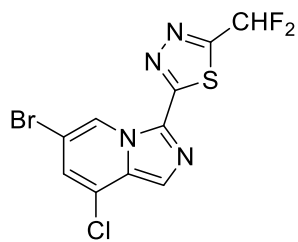
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or



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